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USPT,PGPB,JPAB,EPAB,DWPI	l20 and angiotensin	0	<u>L31</u>
USPT,PGPB,JPAB,EPAB,DWPI	l28 and cre	318	<u>L30</u>
USPT,PGPB,JPAB,EPAB,DWPI	l28 with cre	0	<u>L29</u>
USPT,PGPB,JPAB,EPAB,DWPI	((435/455 435/463 435/320.1 435/325)!CCLS.)	11990	<u>L28</u>
USPT,PGPB,JPAB,EPAB,DWPI	l23 with angiotensin	0	<u>L27</u>
USPT,PGPB,JPAB,EPAB,DWPI	l23 with loxp	0	<u>L26</u>
USPT,PGPB,JPAB,EPAB,DWPI	l23 with cre	0	<u>L25</u>
USPT,PGPB,JPAB,EPAB,DWPI	l23 with (recombinase)	0	<u>L24</u>
USPT,PGPB,JPAB,EPAB,DWPI	((800/18 800/21 800/22 800/25 800/3)!CCLS.)	363	<u>L23</u>
USPT,PGPB,JPAB,EPAB,DWPI	l20 with cre	0	<u>L22</u>
USPT,PGPB,JPAB,EPAB,DWPI	l20 with recombinase	0	<u>L21</u>
USPT,PGPB,JPAB,EPAB,DWPI	capecchi-m\$.in.	20	<u>L20</u>
USPT,PGPB,JPAB,EPAB,DWPI	l18 with cre	0	<u>L19</u>
USPT,PGPB,JPAB,EPAB,DWPI	greer-j.in.	25	<u>L18</u>
USPT,PGPB,JPAB,EPAB,DWPI	bunting-m\$.in.	6	<u>L17</u>
USPT,PGPB,JPAB,EPAB,DWPI	buntin-m\$.in.	0	<u>L16</u>
USPT,PGPB,JPAB,EPAB,DWPI	l14 with cre	0	<u>L15</u>
USPT,PGPB,JPAB,EPAB,DWPI	bernstein-k\$.in.	65	<u>L14</u>
USPT,PGPB,JPAB,EPAB,DWPI	l10 with cre	0	<u>L13</u>
USPT,PGPB,JPAB,EPAB,DWPI	l10 with l6	0	<u>L12</u>
USPT,PGPB,JPAB,EPAB,DWPI	l10 with l7	0	<u>L11</u>
USPT,PGPB,JPAB,EPAB,DWPI	thomas-k\$.in.	507	<u>L10</u>
USPT,PGPB,JPAB,EPAB,DWPI	l7 with excis\$	5	<u>L9</u>
USPT,PGPB,JPAB,EPAB,DWPI	l7 with angiotensin	0	<u>L8</u>
USPT,PGPB,JPAB,EPAB,DWPI	l6 with (gene therapy)	82	<u>L7</u>
USPT,PGPB,JPAB,EPAB,DWPI	l1 with transgen\$	151	<u>L6</u>
USPT,PGPB,JPAB,EPAB,DWPI	l1 and tACE	1	<u>L5</u>
USPT,PGPB,JPAB,EPAB,DWPI	l1 and l2	0	<u>L4</u>
USPT,PGPB,JPAB,EPAB,DWPI	angiotensin	9344	<u>L3</u>
USPT,PGPB,JPAB,EPAB,DWPI	angiotensin with l1	0	<u>L2</u>
USPT,PGPB,JPAB,EPAB,DWPI	cre	1688	<u>L1</u>

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L1 0 CRELOXP

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L2 11929 CRE

=> s transgen?
L3 160055 TRANSGEN?

=> s l2 and l3
L4 1391 L2 AND L3

=> s H and (gene therapy)
L5 61 L4 AND (GENE THERAPY)

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PROCESSING COMPLETED FOR L5
L6 38 DUP REM L5 (23 DUPLICATES REMOVED)

=> d b 1-38 ldb abs

L6 ANSWER 1 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:338738 CAPLUS
DOCUMENT NUMBER: 134:348961
TITLE: Site-specific transgene integration mediated
by a hybrid adenovirus/adenovirus-associated virus vector
using the CreloxP-expression-switching
system

INVENTOR(S): Ueno, Takashi; Matsumura, Hajime; Tanaka, Keiji;
Masaki, Tomoko; Ueno, Mitsuhito; Fujinaga, Kei;
Asada, Kiyoko; Kato, Kunoshin

PATENT ASSIGNEE(S): Takara Shizu Co., Ltd., Japan
SOURCE: PCT Int. Appl., 38 pp.

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE
WO 2001032899 A1 20010510 WO 2000-IP7373 20001023

W. AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,
ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE,
CH, CY,

DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPL. INFO.: JP 1999-308839 A 19991029
AB A method of transferring a transgene into cells, involving the
step of transferring into the cells using an adenovirus vector, a first
nucleic acid having a sequence adeno-sscod, virus-origin inverted
terminal repeats (ITRs) on both sides of the target transgene to
be transferred, and a second nucleic acid having an adeno-sscod,
virus-origin rep gene and a promoter for expressing this gene and
further

carrying a stuffer sequence inserted therein sandwiched between two
recombinase recognition sequences and located between the rep gene
and the promoter, and the step of expressing the Rep protein under the action of
the recombinase in the cells obtained in the above step to thereby integrate
the target foreign gene into the chromosomal DNA, is disclosed. As
vectors, adenoviruses (Ads) have many attractive advantages for in vivo
gene therapy. However, Ads do not usually integrate
into the host genome and gene expression is, thus, transient.
Adeno-sscod, virus (AAV) integrates into a specific locus (AAVS1) on
the human host's chromosome 19, while conventional recombinant AAV
(rAAV)
vectors do not possess this property because such vectors lack the rep
gene. AAV vectors carrying the rep gene do not have enough space for
insertion of a transgene. The authors have constructed hybrid
adenovirus/adeno-sscod, virus (Ad/AAV) vectors which has the
advantages
of both Ads and AAVs for gene transfection. Given that the rep gene
products inhibit propagation of Ads, the authors used the Cre
loxP-expression-switching system to regulate the expression of the rep
gene. In this study, we report the development of three helper-
dependent

adenoviral (HD) vectors, one carrying the Rep8 gene, the other an
AAV-ITR-flanked transgene, and the third for expression of
Cre recombinase gene. The Ad/AAV vectors easily propagate, can
efficiently infect a broad range of cell types, and can integrate into a
specific locus on host chromosomes.

REFERENCE COUNT: 3
REFERENCE(S): (1) Alessandra, R, Proc Natl Acad Sci USA 1999,
V96,

P2615
(2) Takashi, U, Biochemical and Biophysical Research
Communications 2000, V273(2), P473
(3) Yoh, O, Journal of General Virology 1999, V80,
P2477

L6 ANSWER 2 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:12604 CAPLUS
DOCUMENT NUMBER: 134:81749
TITLE: Method for deleting a nucleic acid sequence in a specified tissue from a DNA introduced into the organism
INVENTOR(S): Thomas, Kirk R.; Bernstein, Kenneth E.; Bunting, Michaeline; Greer, Joy; Capocci, Mario
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PXX02
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:
PATENT NO. KIND DATE APPLICATION NO. DATE
WO 2001000809 A1 20010104 WO 2000-US17828 20000629
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 1999-141267 P 19990630
AB The present invention is directed to a method for deleting DNA sequences in a tissue specific manner. In one embodiment, DNA sequences are specifically deleted in germline tissue. In a second embodiment, DNA sequences are specifically deleted in desired somatic tissue. The present invention is further directed to a nucleic acid mol. for use in the method. More specifically, a nucleic acid mol. is provided by the present invention which comprises (a) a recombinase site, (b) a tissue-specific promoter, (c) a recombinase gene, (d) a foreign DNA, and (e) a recombinase site. The nucleic acid mol. may further comprise a gene which is desired to be incorporated into and expressed in a transgenic organism. The method can be used in both plants and animals, and has many applications as described herein.
REFERENCE COUNT: 1
REFERENCES(S): (1) Kilian; Biochemical and Biophysical Research Communications 1996, V222(3), P742 CAPLUS
L6 ANSWER 3 OF 38 MEDLINE
ACCESSION NUMBER: 2001285479 MEDLINE
DOCUMENT NUMBER: 21102048 Pubmed ID: 11157990

TITLE: An inducible mouse model for epidermolysis bullosa simplex
implications for gene therapy.
AUTHOR: Cao T.; Longley M.A.; Wang X.J.; Roop D.R.
CORPORATE SOURCE: Department of Molecular and Cellular Biology, Baylor
College of Medicine, Houston, Texas 77030, USA.
CONTRACT NUMBER: AR62228 (NIAMS)
SOURCE: JOURNAL OF CELL BIOLOGY, (2001 Feb 5) 152 (3) 651-6.
JOURNAL CODE: HMM, 0375356, ISSN: 0021-9525.
PUB. COUNTRY: United States
JOURNAL ARTICLE: (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010529
Last Updated on STN: 20010529
Entered Pubmed: 20010222
Entered Medline: 20010524
AB The Dowling-Mearns variant of epidermolysis bullosa simplex (EBS-DM) is a severe blistering disease inherited in an autosomal-dominant fashion. Here we report the generation of a mouse model that allows focal activation of a mutant keratin 14 allele in epidermal stem cells upon topical administration of an inducer, resulting in EBS phenotypes in treated areas. Using laser capture microdissection, we show that induced blisters healed by migration of surrounding nonphenotypic stem cells into the wound bed. This observation provides an explanation for the lack of mosaic forms of EBS-DM. In addition, we show that decreased mutant keratin 14 expression resulted in normal morphology and functions of the skin. Our results have important implications for gene therapy of EBS and other dominantly inherited diseases.
L6 ANSWER 4 OF 38 EMBASE COPYRIGHT 2001 ELSEVIER SCI.
B.V. DUPLICATE 1
ACCESSION NUMBER: 2001170661 EMBASE
TITLE: Interruption of coding sequences by heterologous introns can enhance the functional expression of recombinant genes.
AUTHOR: Leay-Hubert A.; Thomas R.; Li X.-P.; Lilley C.E.; Coffin R.S.; Roess J.
CORPORATE SOURCE: J. Rees, Department of Medicine, Windeyer Institute of
Medical Sci., University College London, 46 Cleveland Street, London W1P 6DB, United Kingdom
SOURCE: Gene Therapy, (2001) 8(6) (649-653).
Refs: 18
ISSN: 0969-7128 CODEN: GETHEC
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal Article
FILE SEGMENT: 004 Microbiology
022 Human Genetics
029 Clinical Biochemistry

037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Sustained expression of recombinant proteins is a critical factor for the effectiveness of numerous applications in the biomedical sciences including the treatment of human disease by gene therapy. The large scale production of therapeutic proteins, as well as the investigation of gene function by transgenists or cell type specific mutagenesis. Although much attention has been paid to the optimisation of regulatory sequences such as promoters, untranslated regions and polyadenylation signals, effective and sustained expression of recombinant genes in vivo is often difficult to achieve. Here we report that the creation of artificial exons, by insertion of two short heterologous introns into open reading frames, is not only compatible with functional expression, but also leads to a 30-fold enhancement of mRNA production for both green fluorescent protein and the bacteriophage P1-derived Cre recombinase. The levels of green fluorescence were increased five-fold in cell lines and sustained long-term expression at increased levels was observed in rat brain after transduction with a herpes simplex virus-based vector. The data presented identify a means by which the expression of recombinant genes can be enhanced considerably, in addition to and independently from the surrounding regulatory sequences. The method should help obtain sustained and effective expression of recombinant proteins in vivo.
L6 ANSWER 5 OF 38 MEDLINE
ACCESSION NUMBER: 2001285478 MEDLINE
DOCUMENT NUMBER: 21102047 Pubmed ID: 11157999
TITLE: Focal activation of a mutant allele defines the role of stem cells in mosaic skin disorders.
AUTHOR: Ann M.J.; Longley M.A.; Wang X.J.; Roop D.R.
CORPORATE SOURCE: Department of Molecular and Cellular Biology, Baylor
College of Medicine, Houston, Texas 77030, USA.
CONTRACT NUMBER: HD25479 (NICHD)
SOURCE: JOURNAL OF CELL BIOLOGY, (2001 Feb 5) 152 (3) 645-9.
JOURNAL CODE: HMM, 0375356, ISSN: 0021-9525.
PUB. COUNTRY: United States
JOURNAL ARTICLE: (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STN: 20010529
Last Updated on STN: 20010529
Entered Pubmed: 20010222
Entered Medline: 20010524
AB Stem cells are crucial for the formation and maintenance of tissues and organs. The role of stem cells in the pathogenesis of mosaic skin disorders remains unclear. To study the molecular and cellular basis of

mosaicism, we established a mouse model for the autosomal-dominant skin blistering disorder, epidermolytic hyperkeratosis (MIM 113800), which is caused by mutations in either Keratin K1 or K10. This genetic model allows activation of a somatic K10 mutation in epidermal stem cells in a spatially and temporally controlled manner using an inducible Cre recombinase. Our results indicate that lack of selective pressure against certain mutations in epidermal stem cells leads to mosaic phenotypes. This finding has important implications for the development of new strategies for somatic gene therapy of dominant genodermatoses.

L6 ANSWER 6 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
ACCESSION NUMBER: 2001:226197 BIOSIS
DOCUMENT NUMBER: PREV200100226197
TITLE: System for efficient helper-dependent minimal adenovirus construction and rescue.
AUTHOR(S): Hilgenberg, Moritz (1); Schneiders, Frank; Loeser, Peter.
CORPORATE SOURCE: (1) DevelbGen AG, Robert-Roesch-Str. 10, D-13125, Berlin-Buch; mlhilgenberg@hepawc.com Germany
SOURCE: Human Gene Therapy, (April 10, 2001) Vol. 12, No. 6, pp. 643-657, print.
ISSN: 1043-0342
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB: Helper-dependent minimal adenoviral vectors deleted for all viral coding sequences are promising vectors for gene therapy. They retain only the adenovirus cis elements for replication and packaging, can accommodate up to 36 kb of foreign DNA, and exhibit prolonged transgene expression and reduced tissue toxicity as compared with first-generation adenoviral vectors. We have developed a system consisting of a set of cosmid cloning vectors (pMV and pMVX) for simple routine construction and efficient rescue of minimal adenoviral vectors. In the cloning vectors the inverted terminal repeats (ITRs) are flanked by recognition sites for the super rare-cutting endonuclease I-SceI. This allows the release of linear minimal adenovirus genomes for rescue of minimal adenovirus regardless of the sequence of the insert DNA.
pMVX
 contains a multiple cloning site for the insertion of 26 to 36 kb of therapeutic DNA. pMVX contains a noncoding human X-chromosomal DNA fragment as a vector backbone, which provides endonuclease restriction sites that allow for complete or partial replacement of the vector backbone by 1 to 26 kb of therapeutic DNA sequences, while retaining a packageable final minimal adenovirus genome size between 27 and 37.5 kb.
 Both vectors exist in two forms, with or without an Escherichia coli lacZ reporter gene cassette. Several minimal adenoviral vectors with insert

sizes ranging from 1.5 to 16 kb were constructed with these cloning vectors. Minimal adenoviruses were efficiently rescued and amplified to high titers, using a CreIox-based helper system. Vectors containing the X-chromosomal backbone were stable during amplification.
 This simple and efficient system facilitates the construction of minimal adenoviruses and should be useful for further improvement of these new vectors.

L6 ANSWER 7 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:209835 BIOSIS
DOCUMENT NUMBER: PREV200100209835
TITLE: Are we creating problems? Negative effects of Cre recombinase.
AUTHOR(S): Adams, David J. (1); van der Weyden, Louise
CORPORATE SOURCE: (1) Basic and Clinical Genomics Laboratory, Department of Physiology, Institute for Biomedical Research, University of Sydney, Sydney, NSW, 2006; dadams@physiol.usyd.edu.au
SOURCE: Genesis: The Journal of Genetics and Development, (March, 2001) Vol. 29, No. 3, pp. 115, print.
ISSN: 1526-954X
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
L6 ANSWER 8 OF 38 MEDLINE
ACCESSION NUMBER: 2001:167453 MEDLINE
DOCUMENT NUMBER: 21165824 PubMed ID: 11269336
TITLE: Stabilization of transgenes delivered by recombinant adenovirus vectors through extrachromosomal replication.
AUTHOR: Krouglik V A, Krouglik N, Eisensmith R C
CORPORATE SOURCE: Institute for Gene Therapy and Molecular Medicine, Mount Sinai School of Medicine, New York, NY 10029, USA; krouglik01@doc.mssm.edu
CONTRACT NUMBER: DK53333 (NIHDK)
SOURCE: JOURNAL OF GENE MEDICINE, (2001 Jan-Feb) 3 (1) 51-8.
PUB. COUNTRY: England, United Kingdom
Journal Article: (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200105
ENTRY DATE: Entered STM: 20010521
 Last Updated on STM: 20010327
 Entered PubMed: 20010327
 Entered Medline: 20010517
AB: BACKGROUND: A major limitation of adenovirus-mediated gene therapy for metabolic and inherited diseases is the instability of transgene expression in vivo. This instability results, at least

in part, from the inability of the vector genome to maintain the transgene through replication or integration. In this study we evaluated the possibility of stabilization of an adenovirus-delivered transgene by non-adenovirus replicative elements. METHODS: We have developed a novel system for the maintenance of transgenes delivered by adenovirus vectors through extrachromosomal replication. In its initial configuration, this system combines the Epstein-Barr virus (EBV) replicative elements, a tetracycline (Tc)-inducible expression system, and the Cre-loxP recombination system in the context of a single E1/3C4-deleted adenovirus vector. Induction of Cre expression initiates a Cre-mediated recombination, resulting in the excision of a fragment of the vector genome and its circularization into an EBV-based episome. RESULTS: In vitro studies have demonstrated that excision of the circular episome can occur in a cell-free system as well as in cultured cells transfected with plasmid DNA or transduced by virus vector carrying the episome-excising cassette. PCR studies have shown that in proliferating, non-permissive, cultured primate cells the episome generated from the adenovirus vector is maintained much more stably than the genome of the parent vector. This episome was also able to replicate in mammalian cells. CONCLUSION: Together these studies demonstrate the feasibility of this approach for the stabilization of transgenes delivered to dividing cells by adenovirus vectors.

L6 ANSWER 9 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:756892 CAPLUS
DOCUMENT NUMBER: 133:318280
TITLE: Use of retrovirus vectors and the creIox system to achieve efficient, stable, site-specific integration of transforming DNA
INVENTOR(S): Bouthassira, Eric; Lebouche, Philippe
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA; Albert
SOURCE: Einstein College of Medicine of Yeshiva University
PCT Int. Appl., 44 pp.
CODEN: PIXO2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY AOC. NUM. COUNT: 1
PATENT INFORMATION:
PATENT NO. KIND DATE APPLICATION NO. DATE
 WO 2000063410 A1 20001026 WO 2000-US9782 20000412
 W. AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,

DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 1999-293303 A 1 19990416

AB Methods and comps. for transforming cells, resulting in efficient and stable site-specific integration of transgenes, are disclosed.

Transformation is achieved by introducing into a cell an acceptor vector, preferably a retroviral vector, that integrates into the genome of the cell. The acceptor vector comprises two inverted (incompatible) lox sequences, L1 and L2, that differ by a few bases and that cannot recombine with one another. Prior to recombination, the acceptor DNA is preferably integrated into the genome of a cell, such as an embryonic stem cell or

8 fertilized egg. The acceptor DNA optionally may further contain a neg. selectable marker to allow for screening of cells which have undergone the

desired site-specific recombination (e.g., DNA cassette exchange). A donor vector carrying a transgene flanked by the same L1 and L2 sequences and a pos. selectable marker is then introduced into the transformed cells. Stable gene transfer is initiated by cre recombinase-mediated recombination of the lox L1 and L2 sequences.

A retrovirus is used for the first transformation because of its site-specific integration. Any suitable vector, such as an adeno-associat. virus, may be used for the second transformation.

REFERENCE COUNT: 5
REFERENCE(S): (1) Ass Pour Le Dev de La Rech En; FR 2745008 A 1997

CAPLUS

(2) Bouhassira, E, BLOD 1997, V9(9), P3332 CAPLUS
(3) Einstein Coll Med; WO 974758 A 1997 CAPLUS
(4) Feng, Y, JOURNAL OF MOLECULAR BIOLOGY 1999, V292(4), P779 CAPLUS
(5) Genvec Inc; WO 9709439 A 1997 CAPLUS

L6 ANSWER 10 OF 38 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000.756843 CAPLUS

DOCUMENT NUMBER: 133.318273

TITLE: Increased gene expression due to heterologous intron for use in gene therapy or in

obtaining stress resistant transgenic plants

INVENTOR(S): Roes, Jürgen Theodor

PATENT ASSIGNEE(S): University College London, UK

SOURCE: PCT Int. Appl. 40 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 2000063359 A2 20001026 WO 2000-GB1454 20000417

WO 2000063359 A3 20010222

W: AE, AG, AL, AM, AT, AU, AZ, BA, BG, BR, BY, CA, CH, CN,

CR,

CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,

HU,

ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LG, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU,

SD, SE,

SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,

ZW, AM, AZ, BY, BG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH,

CY, DE,

DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,

CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 1999-4788 A 19990416

AB A polynucleotide comprising a coding sequence, which coding sequence comprises a heterologous intron, for use in a method of treatment of the human or animal body by therapy. The intron may be obtained from the mouse

or human Ig-C, mu, or Ig-C, epsilon, genes. A cell, animal or plant comprising the polynucleotide and methods of making such cells, animals or plants are also provided.

L6 ANSWER 11 OF 38 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000.592852 CAPLUS

DOCUMENT NUMBER: 133.173055

TITLE: Helper dependent adenovirus vectors based on site-specific recombinases

INVENTOR(S): Graham, Frank L.; Anton, Martina; Rudnicki, Michael A.

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl. 67 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 2000049168 A2 20000824 WO 2000-US3807 20000215

WO 2000049168 A3 20010301

W: AU, CA, JP

RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,

NL,

PT, SE

PRIORITY APPLN. INFO.: US 1999-251955 A 19990217

US 1999-351819 A 19990713

AB This invention provides helper-dependent adenovirus cloning vectors, helper adenoviruses, and methods for making and using such preps, wherein the helper adenoviruses contain recombinase target sites that are

useful in reducing the level of contamination of helper virus in helper-dependent adenovirus vector preps. The invention is exemplified

using an adenovirus vector with a deletion of all viral coding sequence for the expression of a Epstein gene and its non-packagable helper

adenovirus where its packaging signals within E1 region are flanked on both sides by site-specific recombinase recognition sites, such as lox sites, or FRT sites, or both. Upon the viral infection of the cells expressing high level site-specific recombinase, such as Cre or Flp or both, the packaging signals in helper virus are excised and the helper adenovirus genome is not packaged.

L6 ANSWER 12 OF 38 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000.592850 CAPLUS

DOCUMENT NUMBER: 133.173054

TITLE: A system for production of helper dependent adenovirus vectors based on use of endonucleases

INVENTOR(S): Graham, Frank L.; Ng, Philip; Parks, Robin; Bacchetti,

Sliva; Anglana, Mauro

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl. 97 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 2000049166 A2 20000824 WO 2000-US3771 20000215

WO 2000049166 A3 20010412

W: AU, CA, JP

RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,

NL,

PT, SE

PRIORITY APPLN. INFO.: US 1999-250929 A 19990218

US 1999-475813 A 19991230

AB The present invention relates to methods for efficient and reliable construction of adenovirus vectors which contain and express foreign DNA

and are useful for gene transfer into mammalian cells, for vaccines and for gene therapy. The invention provides for the growth and purification of adenovirus vectors (helper dependent vectors or HDVs) from which all or most of the viral genes have been removed.

The vector system described herein is a new method designed to eliminate helper viruses from the final HDV prep, by cleavage of the helper virus DNA with an endonuclease, alone or in combination with other methods known

to limit the level of helper virus contamination of helper dependent vector preps. The disclosed methods and comps. also provide for regulated control of gene expression. The invention is exemplified by combining recombinase Cre/lox system and restriction endonuclease SmaI system. The SmaI recognition site is placed between two

lox sites flanking the packaging signal, and an internal ITR is inserted to the right of the second lox site. Upon the viral infection of the 293 cells expressing both Cre and SmaI, SmaI can result in a double-stranded break and the adjacent ITR is repaired by paralogous formation (narrowing with the right ITR) to form a replicable DNA lacking the packaging signals. For enhanced safety, the site-specific recombinase

Cre can excise the packaging signals in the heber virus genome and prevent them from being packaged with helper dependent adenovirus vector.

L6 ANSWER 13 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000.441823 CAPLUS
DOCUMENT NUMBER: 133.85169
TITLE: Calcium-dependent transcriptional regulator DREAM and

its cDNA and methods for drug screening
INVENTOR(S): Naranjo Orozco, Jose Ramon, Melstrom, Brit,
Dompebbo

Garcia, Isidro, Link, Wolfgang Alexander, Carion
Rodriguez, Angel Manuel, Lledo Gomez, Francisco
PATENT ASSIGNEE(S): Consejo Superior De Investigaciones
Cientificas, Spain
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: Spanish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 2000037498 A1 20000629 WO 1999-ES402 19991222
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,

CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID,
IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,

MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW,

AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH,

CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

ES 2154201 A1 20010316 ES 1998-2667 19981222
PRIORITY APPLN. INFO.: ES 1998-2667 A 19981222

AB Human DREAM and its cDNA as well as use of DREAM for
transcriptional

silencing of DRE-conig. genes, for regulation of expression of CRE
-dependent genes, and for identification of therapeutic substances, is
disclosed. Thus, expts. demonstrated the repression of DRE-conig.
genes

by DREAM and calcium antagonism of this repression. Further expts.
indicated that DREAM modulated the activity of CRE-conig.
promoters in a calcium-dependent manner via complexes between
DREAM and

CREB and CREM isoforms. The derepression mediated by cAMP and
DRE is specifically mediated by interaction of DREAM and alpha CREM.
Interaction of DREAM with transcription factors binding to CRE

this appears to be a point of interaction of cAMP- and calcium-mediated
intracellular signaling pathways. Mutant forms of DREAM, which bound
to CREB and CREM but did not respond to calcium, blocked the activity of
these proteins.

REFERENCE COUNT: 5
REFERENCES: (1) Camton, A. MOLECULAR AND CELLULAR
BIOLOGY 1998,
V18(12), P6921 CAPLUS

(2) Camton, A. NATURE V398, P80 MEDLINE
(3) Dornetsch, R. NATURE 1997, V386, P855 CAPLUS
(4) Hardingham, G. NATURE 1997, V385, P260 CAPLUS
(5) Meekie, A. NACHR CHEM TECH LAN 1999, V47(6),
P677 CAPLUS

L6 ANSWER 14 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000.161478 CAPLUS
DOCUMENT NUMBER: 132.204060
TITLE: Adenoviruses deleted in the Vdz, 100k and/or

preterminal protein sequences
INVENTOR(S): Amalfitano, Andrea, Chen, Yuan Tsong, Hu, Hui
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 156 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 2000012740 A2 20000309 WO 1999-US19540 19990827
WO 2000012740 A3 20001123

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN,
CU, CZ, DE, DK, DK, EE, ES, FI, GB, GE, GH, GM,

HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD,

SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA,
ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,

CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9956942 A1 20000321 AU 1999-56942 19990827
PRIORITY APPLN. INFO.: US 1998-145742 P 19980828

AB The present invention provides deleted adenovirus vectors. The
inventive
adenovirus vectors carry one or more deletions in the Vdz, 100k,
polymerase and/or preterminal protein sequences of the adenovirus
genome.

In the human adenovirus serotype 5 genomes, such deletions are at
nucleotide positions 4830-5766, 24,950-25,687, and/or 7274-7391. The
adenoviruses may addnl. contain other deletions, mutations or other
modifications as well. In particular preferred embodiments, the

adenovirus genome is multiply deleted, i.e., carries 2 or more deletions
therein. The deleted adenoviruses of the invention are
"propagation-defective" in that the virus cannot replicate and produce
new

virions in the absence of complementing function(s). Preferred
adenovirus
vectors of the invention carry a heterologous nucleotide sequence
encoding
a protein or peptide assocd. with a metabolic disorder, more preferably

a
protein or peptide assocd. with a lysosomal or glycogen storage
disease,
most preferably, a lysosomal acid alpha-glycosidase. The deleted
adenovirus vectors advantageously have an increased carrying capacity

for
heterologous nucleotide sequences, demonstrate lower levels of viral
protein expression, induce fewer host immune responses, and/or exhibit
increased stability and prolonged transgene expression when
introduced into target cells.

L6 ANSWER 15 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000.145009 CAPLUS
DOCUMENT NUMBER: 132.204039
TITLE: Methods and compositions for genomic modification by

site-specific integration
INVENTOR(S): Cabs, Michab P.
PATENT ASSIGNEE(S): The Board of Trustees of the Leland Stanford
Junior
University, USA

SOURCE: PCT Int. Appl., 125 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 2000011155 A1 20000302 WO 1999-US18987 19990819
W: AU, CA, JP

RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,
NL, PT, SE

AU 9956985 A1 20000314 AU 1999-56985 19990819
PRIORITY APPLN. INFO.: US 1998-97166 P 19980819

AB The present invention provides methods of site-specifically integrating
a
polynucleotide sequence of interest in a genome of a eukaryotic cell, as
well as, enzymes, polypeptides, and a variety of vector constructs useful
therefor. In the method, a targeting construct comprises, for example,
(i) a first recombination site and a polynucleotide sequence of interest,
and (ii) a site-specific recombinase, which are introduced into the cell.

The genome of the cell comprises a second recombination site.
Recombination between the first and second recombination sites is
facilitated by the site-specific recombinase. The invention describes
comprns., vectors, and methods of use thereof, for the generation of
transgenic cells, tissues, plants, and animals. The integration

frequency into an attB site located on an EBY plasmid with phage phi C31 integrase/recombinase in mammalian cells is impressively high and several orders of magnitude higher than the frequencies of random integration or homologous recombination, highlighting the utility of this invention. The comps., vectors, and methods of the present invention are also useful in gene therapy techniques.

REFERENCE COUNT: 4

REFERENCE(S): (1) Møller, US 5801030 1998 CAPLUS (2) Reif, US 5830599 A 1998 CAPLUS (3) Sauer, B, Nucleic Acid Research 1996, V24(23), P4608 CAPLUS (4) Weht, US 5654182 A 1997 CAPLUS

L6 ANSWER 16 OF 38 MEDLINE
ACCESSION NUMBER: 2000262155 MEDLINE
DOCUMENT NUMBER: 20262155 PubMed ID: 10800089
TITLE: Functional long-term thymidine kinase suicide gene expression in human T cells using a herpesvirus saimiri vector.

AUTHOR: Hiller, C; Wiltmann, S; Sabin, S; Fickenscher, H
CORPORATE SOURCE: Institut für Klinische und Molekulare Virologie, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

SOURCE: GENE THERAPY, (2000 Apr) 7 (8) 664-74, Journal code: COE: 9421525, ISSN: 0959-7128.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal Article: (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000616
Last Updated on STN: 20000616
Entered Medline: 20000606

AB Herpesvirus saimiri transforms human T lymphocytes to stable growth and persists episomally without genomic integration and without virus production. The transformed T cells retain essential features of their parental cells including the MHC-restricted antigen specificity which may be useful for applications in adoptive immunotherapy. In order to improve the biological safety of such vectors, the prodrug activating gene thymidine kinase of herpes simplex virus was inserted into the genome of herpesvirus saimiri by homologous recombination. After infection with wild-type or cloned recombinant viruses, T cells from tamarin monkeys and from humans were transformed to stable growth. Thymidine kinase-expressing transformed T cells were efficiently eliminated in the presence of low concentrations of ganciclovir. This elimination mechanism remained fully functional over an observation period of 12 months. The potentially immunogenic neomycin resistance gene expression cassette was deleted from the genome of established mutant viruses by using the prokaryotic

CreLoxP recombination system. At any time during the course of a therapeutic application, thymidine kinase-expressing transformed human T cells might be eliminated after administration of ganciclovir. In principle, this function could be useful for the T cell-dependent immunotherapy of resistant blood cancer while avoiding the risk of uncontrolled graft-versus-host disease.

L6 ANSWER 17 OF 38 EMBASE COPYRIGHT 2001 ELSEVIER SCI. BVDUPPLICATE 3
ACCESSION NUMBER: 2000271575 EMBASE
TITLE: Site-specific integration of a transgene mediated by a hybrid adenovirus/adeno-associated virus vector using the CreLoxP-expression-switching system.

AUTHOR: Ueno T.; Matsumura H.; Tanaka K.; Iwasaki T.; Ueno M.; Fujinaga K.; Asada K.; Kato I.
CORPORATE SOURCE: T. Ueno, Biotechnology Research Laboratories, Tahara Shuzo Company, Ltd., Shiga 520-2193, Japan

SOURCE: Biochemical and Biophysical Research Communications, (2000) 273(2) 473-478.
Reis: 30
ISSN: 0006-291X CODEN: BBRC

COUNTRY: United States
DOCUMENT TYPE: Journal Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry

LANGUAGE: English
SUMMARY LANGUAGE: English
AB As vectors, adenoviruses (Ads) have many attractive advantages for in vivo gene therapy. However, Ads do not usually integrate into the host genome and gene expression is, thus, transient. Adeno-associated virus (AAV) integrates into a specific locus (AAVS1) on the human host's chromosome 19, while conventional recombinant AAV (rAAV) vectors do not possess this property because such vectors lack the rep gene. AAV vectors carrying the rep gene do not have enough space for insertion of a transgene. We have constructed a hybrid adenovirus/adeno-associated virus (Ad/AAV) vector which has the advantages of both Ads and AAVs. Given that the rep gene products inhibit propagation of Ads, we used the CreLoxP-expression-switching system to regulate the expression of the rep gene. The Ad/AAV vector easily propagates, can efficiently infect a broad range of cell types, and can integrate into a specific locus on host chromosomes. (C) 2000 Academic Press.

L6 ANSWER 18 OF 38 MEDLINE
ACCESSION NUMBER: 200102826 MEDLINE
DOCUMENT NUMBER: 20480189 PubMed ID: 11024363
TITLE: Site-specific gene targeting for gene expression in eukaryotes.

AUTHOR: Gorman, C; Bullock, C

CORPORATE SOURCE: DNA Bridges, Inc., San Francisco, CA 94117, USA.
cor@dnabridges.com

SOURCE: CURRENT OPINION IN BIOTECHNOLOGY, (2000 Oct) 11 (5) 455-60.
Ref: 39
Journal code: A92, ISSN: 0958-1659

PUB. COUNTRY: ENGLAND: United Kingdom
Journal Article: (JOURNAL ARTICLE)
General Review: (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001113

AB Major advances in the use of site-specific recombinases to facilitate sustained gene expression via chromosomal targeting have been made during the past year. New tools for genomic manipulations using this technology include the discovery of epitopes in recombinases that confer nuclear localization, crystal structures that show the precise topology of recombinase-DNA-substrate synaptic complexes, manipulations of the recognition sequences that select for integration over excision of DNA, and manipulations that make changes in gene expression inducible by drug administration. In addition, endogenous eukaryotic and mammalian DNA sequences have been discovered that can support site-specific recombinase-mediated manipulations.

L6 ANSWER 19 OF 38 LIFESCI COPYRIGHT 2001 CSA
ACCESSION NUMBER: 200054417 LIFESCI
TITLE: Targeted expression of baculovirus p35 caspase inhibitor in oligodendrocytes protects mice against autoimmune-mediated demyelination

AUTHOR: Hisahara, S.; Araki, T.; Sugiyama, F.; Yagami, K.; Suzuki, M.; Abe, K.; Yamamura, K.; Miyazaki, J.; Momoi, T.; Sanita, T.; Bernard, C.C.A.; Okano, H.; Mura, M.
CORPORATE SOURCE: Division of Neuroanatomy, Department of Neuroscience, Biomedical Research Center (D-12), Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan; E-mail: mmura@yama.med.osaka-u.ac.jp

SOURCE: EMBO Journal[EMBO J], (20000201) vol. 19, no. 3, pp. 341-348.
ISSN: 0261-4189

DOCUMENT TYPE: Journal
FILE SEGMENT: G, V, F
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The mechanisms underlying oligodendrocyte (OLG) loss and the precise roles played by OLG death in human demyelinating diseases such as multiple

sclerosis (MS), and in the rodent model of MS, experimental autoimmune encephalomyelitis (EAE), remain to be elucidated. To clarify the involvement of OL G death in EAE, we have generated transgenic mice that express the baculovirus anti-apoptotic protein p35 in OL Gs through the Cre-bxp system. OL Gs from cre/p35 transgenic mice were resistant to tumor necrosis factor- α -, anti-Fas antibody- and interferon- γ -induced cell death, cre /p35 transgenic mice were resistant to EAE induction by immunization with the myelin oligodendrocyte glycoprotein. The numbers of infiltrating T cells and macrophages/microglia in the EAE lesions were significantly reduced, as were the numbers of apoptotic OL Gs expressing the activated form of caspase-3. Thus, inhibition of apoptosis in OL Gs by p35 expression alleviated the severity of the neurological manifestations observed in autoimmune demyelinating diseases.

L6 ANSWER 20 OF 38 MEDLINE
ACCESSION NUMBER: 2000A35689 MEDLINE
DOCUMENT NUMBER: 20393196 Published ID: 10933949
TITLE: Stable transduction of actively dividing cells via a novel adenoviral/episomal vector.
AUTHOR: Lebbis H, Rothe C, Di Fabio N, Orsini C, Yeh P, Paricaudel M
CORPORATE SOURCE: Institut Gustave Roussy, CNRS-IGR-Rhone Poulenc Rorer UMR
SOURCE: 1362, Villejuif, France. lbh@igrf.fr
MOLECULAR THERAPY, (2000 Apr) 1 (4) 314-22.
Journal code: DRT: 100890381, ISSN: 1525-0016.
PUB. COUNTRY: United States
Journal Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journal
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000928
Entered Medline: 20000918

AB Many gene therapy indications would benefit from vectors capable of achieving efficient *in vivo* delivery and long-term transgene expression in either dividing or nondividing cells. Such vector systems are not yet available. To achieve both goals, we have used noncytotoxic E1- and E4-deleted adenoviral vectors as vehicles for delivering an Epstein-Barr virus-based self-replicating episome (replicon) via Cre/bxp site-specific recombination. Co-infection of human cells with a proviralon-encoded and a Cre-expressing adenovirus resulted in efficient delivery and excision of a functional replicon in the absence of vector-induced cytotoxicity. In addition, replication and nuclear retention of the replicon in the cell progeny translated into a prolonged transgene expression in actively dividing cells, both *in vitro* and *in vivo*. Combining desired features from different viruses within a single hybrid vector system should expand the range of clinical indications currently amenable to gene transfer.

L6 ANSWER 21 OF 38 LIFESCI COPYRIGHT 2001 CSA

ACCESSION NUMBER: 2001.27148 LIFESCI
TITLE: Inducible and irreversible control of gene expression using a single transgene
AUTHOR: Vassalli, J.-D.; Herrera, P.L.
M.S.: Furmann-Benzazein, E.; Garcia-Gabay, I.; Pepper, CORPORA TE SOURCE: Department of Morphology and, University of Geneva Medical School, 1 Rue Michel-Servet, CH-1211 Geneva 4, Switzerland.
Email: pedro.herrera@medecine.unige.ch
SOURCE: Nucleic Acids Research [Nucleic Acids Res.], (20001201)
vol. 28, no. 23, e99.
ISSN: 0305-1048.
DOCUMENT TYPE: Journal
FILE SEGMENT: N

LANGUAGE: English
SUMMARY LANGUAGE: English
AB Experimental or therapeutic designs involving the conditional expression of genes often require the use of two different transgenes; this can represent a major undertaking. One of these systems takes advantage of inducible recombinases. Here we show a novel use of such enzymes, in that an inducible recombinase-encoding sequence can function to both block the transcription of a gene placed downstream and, subsequently, irreversibly activate transcription of this very same gene. This double function, which circumvents the need for two transgenes, can be achieved by flanking the inducible recombinase gene by two of its target sequences. In our design we used as the inducible recombinase gene the Cre-ER super(T) gene flanked by two bxp sites. This cassette was placed between a mouse phosphoglycerate kinase promoter and the enhanced green fluorescent protein (EGFP) coding sequence. Mosaic EGFP gene expression in BHK cells bearing this transgene was observed upon administration of 4-hydroxytamoxifen (4-OHT), the inducer of the recombinant activity of Cre-ER super(T). In the absence of 4-OHT EGFP production was prevented. Because of its simplicity (only a single transgene needs to be used) this strategy is of obvious interest in certain protocols of gene or cell therapy and in a variety of experimental designs in which conditional expression of genes is required.

L6 ANSWER 22 OF 38 CARLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999.736961 CARLUS
DOCUMENT NUMBER: 131:347505
TITLE: Novel helper free lentiviral packaging cell lines for use in gene therapy
INVENTOR(S): Leboucq, Philippe; Westerman, Karen
PATENT ASSIGNEE(S): Genetix Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9956701	A1	19991118	WO 1999-US10585	19990513
W. AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, DE, DK, EE, ES, FI, GB, GD, GE, GM, GR, HU, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, NO, RU, TJ, TM				
RW, GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9939887	A1	19991129	AU 1999-39887	19990513
EP 4076715	A1	20010221	EP 1999-923020	19990513
PT, IE, SI, LT, LV, FI, RO				
PRIORITY APPL. IN F.O.:				
WO 1999-US10585	W	19990513		
US 1998-85283	P	19980513		

AB Novel packaging cell lines which produce recombinant retrovirus, free of detectable helper-virus are disclosed. Also disclosed are methods of making the cell lines and methods of producing recombinant retroviruses from the cell lines. Retroviruses produced by the cell lines include lentiviruses, such as HIV, capable of transferring heterologous DNA to a wide range of non-dividing cells. The packaging cells contain at least three vectors which collectively encode retroviral gag, pol, and env proteins, wherein the gag and pol genes are sepd., in part, onto two or more different vectors. This is made possible by fusing Vpr or Vpx to pol.

pol proteins sepd. from gag so that the proteins are targeted to assembling virions. Among other advantages, the packaging cells provide the benefit of increased safety when used in human gene therapy by virtually eliminating the possibility of mol. recombination leading to prodn. of replication-competent helper virus.

REFERENCE(S): (1) Galley, P. WO 9812314 A 1998 CARLUS
(2) Kingsman, A. WO 9817815 A 1998 CARLUS
(3) Richardson, J. Journal of General Virology 1995, 76(3), P691 CARLUS

L6 ANSWER 23 OF 38 CARLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999-360740 CARLUS
DOCUMENT NUMBER: 131:14860
TITLE: Nucleic acids involved in the murine T1-complex Responder phenotype and their diagnostic and

therapeutic applications

INVENTOR(S): Hermann, Bernhard, Koschorz, Birgit, Kierpel, Andreas

PATENT ASSIGNEE(S): Max-Planck-Gesellschaft zur Forderung der Wissenschaften E.V., Germany

SOURCE: PCT Int. Appl., 117 pp.

CODEN: PIXX02

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 9925815 A2 19990527 WO 1998-EP7395 19981118

WO 9925815 A3 19990819

W: AL, AM, AT, AU, AZ, BA, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9916711 A1 19990507 AU 1999-16711 19981118

EP 1032595 A2 20000806 EP 1998-967219 19981118

R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE, IE

PRIORITY APPL. INFO.: EP 1997-120190 A 19971118

EP 1998-103596 A 19980302

WO 1998-EP7395 W 19981118

AB The present invention relates to nucleic acid mo. encoding expression products involved in the Responder function, which contributes to the phenomenon of transmission ratio distortion. The present invention also relates to regulatory regions of the genes corresponding to said nucleic acid mo. The mouse Tr-complex, a region of approx. 12 cM genetic distance on the proximal part of chromosome 17, contains several loci acting in concert to produce a phenomenon called transmission ratio distortion, indicating the fact that the so-called t-haplo type form of this chromosomal region has a selective advantage over the wild type form in that it is transmitted to the offspring at non-Mendelian ratios of up to 99%. The cDNA sequences of T66Bk mo. contain MARK2 kinase and rsk3 kinase homol. regions. T66Bk-2 cDNA contains only the MARK kinase homol. region. T66Bk-8 cDNA contains the complete sequence of T66Bk-2 except for a single base deleted resulting in a frameshift. T66k-7 cDNA corresponds to an antisense transcript of a T66Bk family member, and T66k-20 shows strong similarity to the above members of the T66Bk gene family.

Adonl variants of the T66k family are shown from various mouse strains. The Responder function is located in the T66B region, is expressed in testis, and is expressed during spermiogenesis. Thus, the t-Responder may act as a component of a signaling cascade involved in sperm motility and/or the fertilization of oocytes and relates to methods of influencing transmission ratio. The present invention further relates to recombinant DNA mo. and vectors comprising said nucleic acid mo. and/or regulatory regions as well as to host cells transformed therewith. Adonl, the present invention relates to transgenic animals, comprising said nucleic acid mo., recombinant DNA mo. or vectors stably integrated into their genome. The various embodiments of the invention have a significant impact on breeding strategies by allowing for the specific selection of genetic traits and in particular of sex. Further, the present invention finds applications in the development of contraceptives.

L6 ANSWER 24 OF 38 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999-286096 CAPLUS

DOCUMENT NUMBER: 130-321603

TITLE: Transcriptionally-activated inverted terminal repeats of adeno-associated virus (AAV) for use in recombinant AAV vectors

INVENTOR(S): Fedtkaus, Andrew L.

PATENT ASSIGNEE(S): Targeted Genetics Corporation, USA

SOURCE: PCT Int. Appl. 55 pp

CODEN: PIXX02

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 9920773 A2 19990429 WO 1998-US21937 19981020

WO 9920773 A3 19990701

W: AL, AM, AT, AU, AZ, BA, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9910966 A1 19990510 AU 1999-10966 19981020

EP 1023243 A2 20000809 EP 1998-953639 19981020

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE, MC, PT, IE, FI

PRIORITY APPL. INFO.: US 1997-955400 A 19971021

WO 1998-US21937 W 19981020

AB This invention provides transcriptionally-activated inverted terminal repeats (ITRs) of AAV. The ITRs are less < 400 bp and comprises heterologous transcriptionally active elements which exhibit at least about a two-fold increase in their activities relative to that of a wild-type ITR. These features provide the expression of relatively large transgenes packaged in recombinant AAV vectors for gene therapy. The AAV-derived vector was used to express the human cystic fibrosis transmembrane regulator (CFTR) cDNA.

L6 ANSWER 25 OF 38 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V. DUPLICATE 4

ACCESSION NUMBER: 1999344925 EMBASE

TITLE: Use of helper-dependent adenoviral vectors of alternative serotypes permits repeat vector administration.

AUTHOR: Parks R.J.; Ebleigh C.M.; Graham F.L.

CORPORATE SOURCE: F.L. Graham, Department of Biology, McMaster University,

1280 Main Street West, Hamilton, Ont. L8S 4K1, Canada

SOURCE: Gene Therapy, (1999) 6/9 (1565-1573).

Refs: 74

ISSN: 0969-7128 CODEN: GETHEC

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal Article

FILE SEGMENT: 004 Microbiology

022 Human Genetics

LANGUAGE: English

SUMMARY LANGUAGE: English

AB We have developed a new helper adenovirus (Ad) based on serotype 2.

Ad2L C8c-CARP, for use in the Cre/loxP system to generate Ad vectors deleted of all protein coding sequences (helper-dependent Ad vectors (hdAd)). A comparison of Ad2L C8c-CARP and our original helper virus

(based on serotype 5, Ad5L C8cLup) showed that the two helper viruses amplified hdAd with a similar efficiency, and resulted in a similar yield and purity after large-scale preparation of vector. In vitro, the resulting hdAd2 had a similar transduction efficiency and expression kinetics of transgene (beta-gal) as the hdAd5. An important feature of the helper-dependent system is that all virus components, except the virus DNA, derive from the helper virus. Consequently, vectors produced with help from Ad2L C8c-CARP were not neutralized by antibodies against Ad5, and vectors produced with Ad5 helper were resistant to neutralizing antibodies against Ad2. Analysis of transgene expression in mouse liver after intravenous injection of the Ad2-based hdAd showed that the vector could efficiently transduce the liver and produce high levels of a foreign transgene, similar to those expressed by the hdAd generated with the Ad5 helper virus. Mice immunized with hdAd2 produced Ad2-neutralizing antibodies, which did not cross-react with hdAd5.

To determine if successful repeat Ad vector administration could be achieved by sequential use of alternative Ad serotypes, we injected mice with hdAd2 (hSEAP) followed 3 months later by a beta2-expressing hdAd4 of either the same or different serotype. Repeated administration of hdAd2 resulted in a 30- to 100-fold reduction in

transgene expression compared with naïve animals. In contrast, no decrease in transgene expression was observed when the second vector was of a different serotype. These results demonstrate that effective vector readministration can be achieved by the sequential use of

hdads based on alternative serotypes.

L6 ANSWER 26 OF 38 LIFESCI COPYRIGHT 2001 CSA

ACCESSION NUMBER: 1999/72103 LIFESCI

TITLE:

Impaired myocardial angiogenesis and ischemic cardiomyopathy in mice lacking the vascular endothelial growth factor isoforms VEGF sub(164) and VEGF sub(188)

AUTHOR:

Brusse-Hartnug, K.; Cornelissen, I.; Eber, E.; Kalkar, V.V.; Stalmans, I.; Maitot, V.; Pennard, J.-C.; Dewerchin, M.; Fleming, W.; Nagy, A., et al.

CORPORATE SOURCE: The Center for Transgene Technology and Gene Therapy.

Flanders Interniversity Institute for Biotechnology, KU Leuven, Leuven, B-3000, Belgium; E-mail: peter.cornelissen@med.kulbvuven.ac.be

SOURCE: Nature Medicine [Nat. Med.], (1999)3(50) vol 5, no. 5, pp.

495-502, ISSN: 1078-8956.

DOCUMENT TYPE: Journal

FILE SEGMENT: W3.G

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The gene for vascular endothelial growth factor (VEGF) encodes three

spliced isoforms. Although the heparin binding capacities of these isoforms differ, little is known about their differential functions in

who. We generated mice expressing exclusively the VEGF sub(120)

isoform

(VEGF super(120/120) mice) by Cre/loxP-mediated removal of exons

6 and 7, which encode the isoforms of 164 and 188 amino acids. VEGF

super(120/120) mice had impaired postnatal myocardial angiogenesis,

resulting in ischemic cardiomyopathy characterized by reduced

contractility and sarcomere breakdown, but normal stores of high-

energy

phosphates. VEGF super(120/120) mice ultimately died of cardiac

failure.

The VEGF super(120/120) mouse model may be useful for studying the

molecular mechanisms of the myocardial response to ischemia and for

testing the angiogenic properties of different VEGF isoforms. Vascular

endothelial growth factor (VEGF) is involved in embryonic and

pathological

vascular development. It may also be involved in the angiogenic

response

to myocardial ischemia and is now being tested for use in gene

therapy of ischemic heart and tissue diseases. The mouse VEGF gene

is alternatively transcribed to produce at least three isoforms: VEGF

sub(120), VEGF sub(164) and VEGF sub(188). VEGF sub(120) is

diffusible in

the extracellular milieu, whereas the longer isoforms show increasing

binding to heparan sulfate-rich matrix. These isoforms differ in their

mitogenicity, chemotactic properties, receptor binding characteristics

and

issue-specific expression. However, it remains controversial whether

the isoforms differ in specificity, potency or quality for their role in

normal, pathological or therapeutic angiogenesis in vivo. Nevertheless,

gene therapy protocols now use VEGF sub(120) or VEGF

sub(164) indiscriminately for improvement of tissue ischemia. As the

loss

of a single VEGF allele results in embryonic lethality due to severe

vascular defects, it is not possible to study the role of VEGF during

postnatal angiogenic processes by conventional transgene

technology. Therefore, we generated mice expressing only VEGF

sub(120)

(VEGF super(120/120) mice) using the Cre/loxP system to remove

exons 6 and 7, which encode basic domains that are only present in

VEGF

sub(164) and/or VEGF sub(188). The absence of VEGF sub(164) and

sub(188) impaired myocardial angiogenesis, leading to ischemic

cardiomyopathy.

L6 ANSWER 27 OF 38 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998/176034 CAPLUS

DOCUMENT NUMBER: 128.214185

TITLE: Use of the cre-loxP system to control

expression of genes in the manufacture of adenovirus

vectors for gene therapy

INVENTOR(S): Wilson, James M.; Phaneuf, Daniel

PATENT ASSIGNEE(S): Trustees of the University of Pennsylvania,

USA.

SOURCE: Wilson, James M.; Phaneuf, Daniel

PCIT Int. Appl. 49 pp.

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY AOC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 9810086 A1 19980312 WO 1997-US15691 19970904

W. AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,

DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ,

LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,

PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG,

US, UZ, VN, YU, ZW, AM, AZ, BY, BG, KZ, MD, RU, TJ, TM,

RW, GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,

FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,

GN, ML, MR, NE, SN, TD, TG AU 1997-41830 19970904

AU 9741830 A1 19980326 AU 1997-41830 19970904

AU 722375 B2 20000803 EP 1997-939821 19970904

EP 930111 A1 19991020 EP 1997-939821 19970904

R, AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE, MC,

PT, IE, FI

JP 2001500014 T2 20010109 JP 1998-512948 19970904

PRIORITY APPL. INFO.: US 1996-26323 P 19960906

WO 1997-US15691 W 19970904

AB A method for the manu. of adeno-assoc. virus carrying a foreign

gene in

which the cre-loxP system is used to regulate expression of the

replicap genes is described. Regulated expression of these genes

allows

efficient packaging of a gene flanked by adeno-assoc. virus inverted

terminal repeats without a build up of toxic levels of the rep gene

product. The method uses three vectors. A first vector is an expression

vector for the cre gene, the second is an expression vector for

the replicap genes in which the promoter is sepd. from the coding region

by

an insert flanked by loxP sites and replicap, and a third vector contains a

minigene coding, a transgene and regulatory sequences flanked by

AAV ITRs. The third vector contains an expression cassette for the

therapeutic gene flanked by AAV inverted terminal repeats. The host

cell

stably or inducibly expresses the cre gene and two vectors

carrying the other elements of the system are introduced into the host

cell

L6 ANSWER 28 OF 38 EMBASE COPYRIGHT 2001 ELSEVIER SCI.

B.V DUPLICATE 5

ACCESSION NUMBER: 1998236963 EMBASE

TITLE: An adenoviral vector deleted for all viral coding sequences

results in enhanced safety and extended expression of a

loxp transgene.

AUTHOR: Morsy M.A.; Gu M.; Meizel S.; Zhao J.; Lin J.; Su Q.;

Allen

H.; Franlin L.; Parks R.J.; Graham F.L.; Kochanek S.; Batt

A.J.; Caskey C.T.

CORPORATE SOURCE: M.A. Morsy, Department of Human Genetics,

Merck Research

Laboratories, West Point, PA 19486, United States.

SOURCE: Proceedings of the National Academy of Sciences of the

United States of America, (7 Jul 1998) 95(14 (7866-7871).

Refs: 36

ISSN: 0027-8424 CODEN: PNAS-6

COUNTRY: United States

DOCUMENT TYPE: Journal Article

FILE SEGMENT: 004 Microbiology

022 Human Genetics

029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Adenoviral (Ad)-mediated in vivo gene transfer and expression are

limited

in part by cellular immune responses to viral-encoded proteins and/or

transgene immunogenicity. In an attempt to diminish the former

responses, we have previously developed and described helper-

propagated in a Cre recombinase-based system, and can be produced to high concentration and purity (>99.9% helper-free vector). In this study, we compared safety and efficacy of leptin gene delivery mediated by an HD vector (HD-leptin) and a first-generation E1-deleted Ad vector (Ad-leptin) in normal lean and ob/ob (leptin-deficient) mice. In contrast to evidence of liver toxicity, inflammation, and cellular infiltration observed with Ad-leptin delivery in mice, HD-leptin delivery was associated with a significant improvement in associated safety/toxicity and resulted in efficient gene delivery, prolonged elevation of serum leptin levels, and associated weight loss. The greater safety, efficient gene delivery, and increased insert capacity of HD vectors are significant improvements over current Ad vectors and represent favorable features especially for clinical gene therapy applications.

L6 ANSWER 29 OF 38 BIOSIS COPYRIGHT 2001 BIOSIS
DUPPLICATE 6
ACCESSION NUMBER: 1998-404618 BIOSIS
DOCUMENT NUMBER: PRE/19980404618
TITLE: Efficient Fas-Igand gene expression in rodent liver after intravenous injection of a recombinant adenovirus by the use of a Cre-mediated switching system.
AUTHOR(S): Okuyama, T. (1); Fujino, M.; Li, X.-K.; Funeshima, N.; Kasuga, M.; Saito, I.; Suzuki, S.; Yamada, M.
CORPORATE SOURCE: (1) Dep. Genet., Natl. Child. Med. Res. Cent., 3-35-31
SOURCE: Teshido, Setagaya-ku, Tokyo 154-8509 Japan
ISSN: 0969-7128.
DOCUMENT TYPE: Article
LANGUAGE: English
AB: An adenovirus vector AxCALNfasl was constructed in order to transduce a gene for rat Fas-Igand, requiring co-expression of Cre recombinase for its expression. In the cosmid cassette, pAxCALNfasl, a stuffer DNA fragment flanked with two bxp sequences was placed between the promoter and Fas-Igand cDNA to prevent its expression in transduced 293 cells. COS-7 cells infected with AxCALNfasl alone did not induce apoptosis in cocultivated Jurkat cells, but the cells treated with AxCALNfasl and AxCANCre (an adenovirus expressing Cre recombinase with the CAG promoter) did. BALB/c mice injected with plaque-forming units of AxCALNfasl and with different doses of AxCANCre, developed lethal acute liver failure. The number of the apoptotic hepatocytes increased dramatically with increased doses of injected AxCANCre, indicating that the level of transgene expression in the rodent liver appeared to be adjustable. Based on these observations, we conclude that vectors expressing a gene to produce cytotoxic substances

can be constructed by the use of a Cre-mediated switching system. Our system also demonstrated that efficient expression of the toxic gene in the rodent liver was achievable by co-injection of adenovirus vectors carrying the target gene and Cre recombinase.

L6 ANSWER 30 OF 38 LIFESCI COPYRIGHT 2001 CSA
ACCESSION NUMBER: 1998-79662 LIFESCI
TITLE: Generation of a conditionally neo super(f)-containing retroviral producer cell line: effects of neo super(f) on retroviral titer and transgene expression
AUTHOR: Wiltinger, O.; Candolfi, F.; Kieckhef, E.G.; Xenitopoulos, K.G.; Ramsey, W.J.; Biese, R.M.
CORPORATE SOURCE: Clinical Gene Therapy Branch, NHGRI, NIH, Building 10, Room 10C103, 10 Center Drive, MSC 1851, Bethesda, MD, 20892-1851 USA
SOURCE: Gene Ther., (19980500) vol 5, no 5, pp 664-691.
ISSN: 0969-7128.
DOCUMENT TYPE: Journal
FILE SEGMENT: W3
LANGUAGE: English
SUMMARY LANGUAGE: English
AB: We have developed a method for generating high-titer retroviral cell lines conditionally containing a neomycin resistance gene (neo super(f)) based on the CreLoxP system. For this, a bidirectional retroviral splicing vector carrying the green fluorescence protein (GFP) and a marker gene cassette consisting of internal ribosome entry site (IRES) and neo super(f) flanked by bxp sites, was constructed and conveniently used to generate a G418 resistant vector producer cell line.
 Following titer determination and verification of the biological activity of the retroviral supernatants, the selectable expression cassette which was no longer required was excised from the provirus by transient Cre expression using an adenoviral vector. This strategy led to precise excision of neo super(f) and generation of retroviral supernatants containing functional 'neo-less' retroviral particles without detrimental effects on the high vector titers found in the parental neo super(f)-containing producer lines. GFP expression was significantly increased after the excision of neo super(f), in both the producer lines and retrovirally transduced target cells. Reintroduction of neo super(f) did not alter GFP expression, suggesting that the neo super(f) gene and/or its gene product per se are not acting as a transcriptional silencer.

L6 ANSWER 31 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998-15660 CAPLUS
DOCUMENT NUMBER: 128-85158
TITLE: Use of retrovirus vectors and the crelox system to achieve efficient, stable, site-specific integration of transforming DNA
INVENTOR(S): Leibovich, Philippe; Boulassra, Eric; Westerman, Karen; Takekoshi, Ken Julian
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA; Albert Einstein College of Medicine of Yeshiva University
SOURCE: PCT Int. Appl., 24 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 97/47758	A1	1997/12/18	WO 1997-US9954	1997/06/06	
W. AL, AM, AT, AU, AZ, BA, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, RW, GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GR, IE, IT, LU, MC, NL, PT, SE, BF, BU, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG	US 5928914	A	19990727	US 1996-743796	19961105
CA 2258007	AA	19971218	CA 1997-2258007	19970606	
AU 9733062	A1	19980107	AU 1997-33062	19970606	
AU 733016	B2	20010503			
EP 914457	A1	19990512	EP 1997-928910	19970606	
R. AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI	JP 2000512150	T2	20000919	JP 1998-501738	19970606
PRIORITY APPL. INFO:	US 1996-664084	A	19960514		
US 1996-743796	A	19961105			
WO 1997-US9954	W	19970606			

AB: A transformation method that results in efficient and stable site-specific integration of transforming DNA is described. Transformation is achieved by introducing into a cell an acceptor vector, preferably a retroviral vector, that integrates into the genome of the cell. The acceptor vector comprises two incompatible bx sequences, L1 and L2, that differ by a few bases and that cannot recombine with one another. A donor vector carrying a transgene flanked by the same L1 and L2 sequences is then introduced into the transformed cells. Stable gene transfer is initiated by cre recombinase-mediated recombination of the bx L1 and L2 sequences. A retrovirus is used for the first transformation because of its site-specific integration. Any suitable vector, such as an adenovirus, may be used for the second transformation.

L6 ANSWER 32 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997-579821 CAPLUS
DOCUMENT NUMBER: 127-243992
TITLE: Glucocorticoid receptor with modified ligand specificity, fusion proteins confining the ligand binding domain thereof, and their use in controlling gene expression in recombinant cells and transgenic animals

INVENTOR(S): Brocard, Jacques Bertrand; Chambon, Pierre Henri;
Gronemeyer, Hirsch; Metzger, Daniel Nicolas;
Jean-Claude, Roux, Sylvie
PATENT ASSIGNEE(S): Association pour le Développement de la
Recherche,
F.; Brocard, Jacques Bertrand; Chambon, Pierre Henri;
Gronemeyer, Hirsch; Metzger, Daniel Nicolas;
Jean-Claude, Roux, Sylvie
PCT Int. Appl. 99 pp.
SOURCE: CODEN: PIXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9731108	A1	19970828	WO 1997-FR315	19970220
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
FR 2745008	A1	19970822	FR 1996-2060	19960220
CA 2247517	AA	19970828	CA 1997-2247517	19970220
AU 9720989	A1	19970910	AU 1997-20989	19970220
AU 70784	B2	19990715		
EP 886620	A1	19990217	EP 1997-906232	19970220
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE, MC, PT, IE, FI				
JP 2000505298	T2	20000509	JP 1997-529854	19970220
PRIORITY APPL. INFO.: FR 1996-2060				19960220
WO 1997-FR315				19970220

AB A DNA fragment coding for a modified nuclear glucocorticoid receptor, particularly one mutated in the region coding for the ligand binding domain, so that receptor activity is more strongly inducible by a synthetic glucocorticoid ligand than by a natural glucocorticoid ligand, is disclosed. A fusion protein between the modified ligand-binding domain of the glucocorticoid receptor and a DNA-binding domain may be used to control gene expression in recombinant cells or in transgenic animals. A recombination system inducible in mammals by means of a fusion protein produced between a recombinase and the binding domain of the ligand derived from the modified glucocorticoid receptor of which the activity is more strongly inducible by synthetic glucocorticoids than by natural glucocorticoids, is also disclosed. The human glucocorticoid receptor config. threonine at position 747 instead of isoleucine displays normal transactivating activity with dexamethasone, but not with natural ligands aldosterone and corticosterone. COS-7 cells config. a reporter gene controlled by a GRE were exposed to dexamethasone or corticosterone.
Reporter gene expression was only obsd. with the synthetic glucocorticoid.
Control of genetic recombination (i.e. excision of loxP-flanked gene insert) in cells or transgenic mice by modified glucocorticoid receptor ligand binding domain fused to Cre recombinase was also demonstrated.

L6 ANSWER 33 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996.601803 CAPLUS
DOCUMENT NUMBER: 125.240227
TITLE: Materials and methods for regulating polypeptide production in animal cells and their clinical application
INVENTOR(S): Thorens, Bernard
PATENT ASSIGNEE(S): Ecole Polytechnique Federale De Lausanne, Switz.,
Universite De Lausanne, Centre Hospitalier
Universitaire Vaudois, Kiddle, Simon John
PCT Int. Appl. 29 pp.
SOURCE: CODEN: PIXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9625487	A1	19960822	WO 1996-GB256	19960207
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, CA, GN, ML, MR, NE				
CA 2211101	AA	19960822	CA 1996-2211101	19960207
AU 9646295	A1	19960904	AU 1996-46295	19960207
AU 699061	B2	19981119		
EP 809692	A1	19971203	EP 1996-901901	19960207
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE, MC, PT, IE				
JP 11505102	T2	19960518	JP 1996-524735	19960207
US 6074875	A	20000613	US 1998-912946	19980304
PRIORITY APPL. INFO.: GB 1996-2830				A 19960214
WO 1996-GB256				W 19960207

AB This application relates to cell lines transfected with (a) nucleic acid encoding one or more hormone receptors, the receptors being capable of transmitting a signal, and (b) nucleic acid encoding a desired polypeptide, the nucleic acid encoding the polypeptide being under the control of a promoter config. regulatory elements (e.g. CRE) responsive to the signal transmitted by the receptor(s) so that transcription of the nucleic acid encoding the desired polypeptide is modulated by the level of the hormone(s) in the patient. Preferably, the receptors are the GIP (gastric inhibitory polypeptide) or GLP-1 (glucagon-related peptide 1) receptors controlling the prodn. of insulin in the cells in response to changes in the metabolic status of a patient. The methods are useful in controlling metabolic diseases such as type I or type II diabetes or obesity.

L6 ANSWER 34 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996.360220 CAPLUS
DOCUMENT NUMBER: 125.27701
TITLE: Regulatable elimination of gene expression, gene product function and engineered host cells, and its application in gene therapy
INVENTOR(S): Brugge, Joan S.; Cadirene, Gerald R.
PATENT ASSIGNEE(S): Aired Gene Therapeutics, Inc., USA
SOURCE: PCT Int. Appl. 141 pp.
CODEN: PIXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9606111	A1	19960229	WO 1995-US10591	19950818
W: AU, CA, GB, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5834286	A	19981110	US 1994-292597	19940818
AU 9534092	A1	19960314	AU 1995-34092	19950818
EP 776335	A1	19970604	EP 1995-93068	19950818
R: AT, CH, DE, FR, GB, LI, SE				
JP 10507624	T2	19980728	JP 1995-508238	19950818
PRIORITY APPL. INFO.: US 1994-292595				A 19940818
US 1994-292596				A 19940818
US 1994-292597				A 19940818
US 1993-17931	B2	19930212		
US 1993-92977	B2	19930716		
US 1993-93499	A2	19930716		
US 1994-179143	B2	19940107		
US 1994-179748	A2	19940107		
WO 1995-US10591				W 19950818

AB Materials and methods are disclosed for regulated obstruction of the expression of a target gene or the hol effect of its gene product in genetically engineered cells or organisms config. them. Aspects of the invention are exemplified by recombinant modifications of host cells and their use in vitro and in vivo for the regulatable blockade of expression of a target gene, for interference with the function or effect of a target gene product or for the regulatable elimination of a target gene. Synthesis of oligomer of ligands such as FK506 and cyclosporin A, and regulation of programmed cell death with immunophilin-Fas antigen chimerae were demonstrated.

L6 ANSWER 35 OF 38 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996.524191 CAPLUS
DOCUMENT NUMBER: 125.213589
TITLE: Reversible immortalization of mammalian cells mediated by retroviral transfer and site-specific recombination
AUTHOR(S): Westerman, Karen A.; Lehoucq, Philippe
CORPORATE SOURCE: Div. Health Sciences Technology, Massachussets Inst.
SOURCE: Technology, Cambridge, MA, 02139, USA
Proc. Natl. Acad. Sci. U. S. A. (1996), 93(17), 8971-8976

CODEN: PNASAB; ISSN: 0027-8424

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A procedure of reversible immortalization of primary cells was devised by

retrovirus-mediated transfer of an oncogene that could be subsequently excised by site-specific recombination. This study focused on the early stages of immortalization, global induction of proliferation and the span extension of cell populations. Comparative anal. of Cre/LoxP and FL/PTFRT recombination in this system indicated that only Cre/LoxP operates efficiently in primary cells. Cells reverted to their preimmortalized state, as indicated by changes in growth characteristics and p53 levels, and their fate conformed to the telomere hypothesis of replicative cell senescence. By permitting temporary and controlled expansion of primary cell populations without retaining the transferred oncogene, this strategy may facilitate gene therapy manipulations of cells unresponsive to exogenous growth factors and make practical gene targeting by homologous recombination in somatic cells. The combination of retroviral transfer and site-specific recombination should also extend gene expression studies to situations previously inaccessible to experimentation.

L6 ANSWER 38 OF 38 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 7

ACCESSION NUMBER: 96344509 EMBASE

DOCUMENT NUMBER: 1996344509

TITLE: Recombinant adenoviruses with large deletions generated by

Cre-mediated excision exhibit different biological properties compared with first-generation vectors in vitro and in vivo.

AUTHOR: Lieber A.; He C.-Y.; Krilova I.; Key M.A.

CORPORATE SOURCE: Division of Medical Genetics, Department of Medicine, University of Washington, Seattle, WA 98195, United States

SOURCE: Journal of Virology, (1996) 70/12 (8944-8950).

ISSN: 0022-538X CODEN: JOVIAM

COUNTRY: United States

DOCUMENT TYPE: Journal Article

FILE SEGMENT: 004 Microbiology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB In vivo gene transfer of recombinant E1-deficient adenoviruses results in early and late viral gene expression that elicits a host immune response, limiting the duration of transgene expression and the use of adenoviruses for gene therapy. The prokaryotic Cre-lox P recombination system was adapted to generate recombinant adenoviruses with extended deletions in the viral genome (referred to here as deleted viruses) in order to minimize expression of immunogenic

and/or cytotoxic viral proteins. As an example, an adenovirus with a 25-kb deletion that lacked E1, E2, E3, and late gene expression with viral titers similar to those achieved with first-generation vectors and less than 0.5% contamination with E1-deficient virus was produced. Gene transfer was similar in HeLa cells, mouse hepatoma cells, and primary

mouse hepatocytes in vitro and in vivo as determined by measuring reporter gene expression and DNA transfer. However, transgene expression and deleted viral DNA concentrations were not stable and declined to undetectable levels much more rapidly than those found for

first-generation vectors. Intravenous administration of deleted vectors in mice resulted in no hepatocellular injury relative to that seen with first-generation vectors. The mechanism for stability of first-generation adenovirus vectors (E1a deleted) appeared to be linked in part to their ability to replicate in transduced cells in vivo and in vitro. Furthermore, the deleted vectors were stabilized in the presence of undelivered first-generation adenovirus vectors. These results have important consequences for the development of these and other nonintegrating vectors for gene therapy.

L6 ANSWER 37 OF 38 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1996054426 CAPLUS

DOCUMENT NUMBER: 125294260

TITLE: Regulable promoters for use in gene

therapy applications: Modification of the 5'-flanking region of the C-TR gene with multiple cAMP response elements to support basal, low-level gene expression that can be upregulated by exogenous agents that raise intracellular levels of cAMP

AUTHOR(S): Suzuki, Motoyoshi; Singh, Ravi N.; Crystal, Ronald

G. CORPORATE SOURCE: Cornell Medical Center, New York Hospital, New York, NY, 10021, USA

SOURCE: Hum. Gene Ther., (1996) 7/15, 1863-1893

CODEN: HGTHE3; ISSN: 1043-0342

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This study focuses on the design, construction, and evaluation of a chimeric promoter for gene therapy applications where it is desirable to have low-level basal expression of the newly transferred gene, which can be induced to higher levels of expression by the administration of pharmacol. agents that can be safely used locally and/or systemically in humans. To achieve this, a chimeric promoter

was constructed using fragments of the 5'-flanking region of the human cystic fibrosis transmembrane conductance regulator (C-TR) gene, and multiple tandem repeats of the consensus sequence and flanking elements of the cAMP response element (CRE), promoter sequences that support increased transcription in response to elevations in intracellular cAMP levels. Preliminary studies using plasmid vectors demonstrated that: (i) the 5'-flanking sequences from the C-TR gene have low promoter activity in the human airway epithelial cell lines; (ii) chimeras using 7-18 bp fragment from the 5'-flanking sequence of C-TR gene as the base, with

the addn. of 4-10 units of a 25-bp sequence containing the CRE consensus sequence, were all inducible by a rise in intracellular cAMP, with the chimera having eight CRE repeats the most responsive; and (iii)

a CF 126(CREB) chimera, consisting of the -126 bp fragment from the 5'-flanking region of C-TR gene together with eight CRE repeats, yielded low-level basal activity but maximal upregulation by cAMP, resulting in expression of the reporter gene that was 51-58% of an RSV-

LTR control. On the basis of these observations, replication-deficient adenoviral vectors containing the CF 126(CREB) chimera and the luciferase reporter gene [AdCF 126(CREB)Luc] or the Escherichia coli lacZ (beta-Gal) reporter gene [AdCF 126(CREB)beta gal] were constructed. In several human airway epithelial cell lines, the AdCF 126 (CRE

)Luc vector provided low basal activity, but was significantly upregulated by agents that increase cAMP levels. Intranasal administration of the beta-Gal-expressing AdCF 126(CREB) beta gal vector into C57B/16 mice demonstrated cAMP-induced upregulation of the

reporter gene in airway epithelial cells. Quantification of the inducibility of the chimeric promoter activity in the airway epithelium using the AdCF 126(CREB)Luc vector demonstrated an 11-fold upregulation of the basal promoter activity in the lung with the administration of a phosphodiesterase inhibitor and a cAMP analog. These observations

demonstrate the feasibility of using a chimeric promoter comprised of a minimal fragment of the C-TR 5'-flanking region, together with added multiple CRE, to control genes delivered in vivo. Importantly, because there are many drugs used in humans that raise cAMP, the concept of using a cAMP-regulatable promoter may also be a useful approach to enhance the safety, efficacy, and feasibility of a variety of human gene therapy strategies.

L6 ANSWER 38 OF 38 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 8

ACCESSION NUMBER: 92102575 EMBASE

DOCUMENT NUMBER: 1992102575

TITLE:

Identification of cryptic box sites in the yeast genome by selection for Cre-mediated chromosome translocations that confer multiple drug resistance.

AUTHOR: Sauer B.

CORPORATE SOURCE: Du Pont-Merck Pharmaceutical Co., Experimental Station

E328 Wilmington, DE 19880-0328, United States

SOURCE: Journal of Molecular Biology, (1992) 223/4 (911-928).

ISSN: 0022-2836 CODEN: JMOBAK

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal Article

FILE SEGMENT: 004 Microbiology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The Cre recombinase efficiently causes site-specific DNA recombination at bxp sites placed into the eukaryotic genome. Since the bxp site of phage P1 is 34 base-pairs in size, the natural occurrence of this exact sequence is unlikely in any eukaryotic genome. However, related sequences may exist in eukaryotic genomes that could recombine at

bw
efficiency with an authentic bxp site. This work identifies such cryptic bxp sites in the yeast genome using a positive selection procedure that allows the detection of events occurring at a frequency of $< 1 \times 10^{-7}$. The selection is based on the disruption/reconstruction of the yeast gene YGL022. Disruption of YGL022 confers multiple drug sensitivity. Recombination events at a bxp site 5' to the structural gene restore expression of YGL022 and result in a multiple drug resistant phenotype. These drug resistant mutants all display chromosomal rearrangements resulting from bw-frequency Cre-mediated recombination with an endogenous cryptic bxp site. Ten such sites have been found and they have been mapped physically to a number of different yeast chromosomes. Although the efficiency of Cre-mediated recombination between bxp and such endogenous sites is quite low, it may be possible to redesign recombination substrates to improve recombination efficiency. Because of the greater complexity of the human and mouse genomes compared with yeast an analogous situation is likely to exist in these organisms. The availability of such sites would be quite useful in the development of alternative strategies for gene therapy and in the generation of transgenic animals.

=> d tms

(FILE HOME ENTERED AT 09:18:04 ON 08 JUN 2001)

FILE EMBASE, BIOSIS, LIFESCI, MEDLINE, CAPLUS ENTERED AT 09:18:45 ON 08 JUN 2001

L1 0 S CRELOXP
L2 11929 S CRE
L3 180055 S TRANSGEN?
L4 1391 S L2 AND L3
L5 61 S L4 AND (GENE THERAPY)
L6 38 DUP REM L5 (23 DUPLICATES REMOVED)

=> s M and IAGE
L7 0 L4 AND TAGE

=> s M and angiotensin
L8 24 L4 AND ANGIOTENSIN

=> dup rem B
PROCESSING COMPLETED FOR L8
L9 9 DUP REM L8 (15 DUPLICATES REMOVED)

=> d B 1-9 ibib abs

L9 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999.350740 CAPLUS
DOCUMENT NUMBER: 131:14860
TITLE: Nucleic acids involved in the murine T4-complex
Responder phenotype and their diagnostic and therapeutic applications
INVENTOR(S): Hermann, Bernhard; Koschitz, Birgit; Kispert, Andreas

PATENT ASSIGNEE(S): Max-Planck-Gesellschaft zur Forderung der Wissenschaften E.V., Germany
SOURCE: PCT Int. Appl. 117 pp.
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY AOC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9925815	A2	19990527	WO 1998-EP7395	19981118
WO 9925815	A3	19990819		
W. AL, AM, AT, AU, AZ, BA, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, GR, GU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, CA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9916711	A1	19990607	AU 1999-16711	19981118
EP 1032595	A2	20000906	EP 1998-961219	19981118
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE, IE				
EP 1998-103595	A	19980302	EP 1997-120190	A 19971118
PRIORITY APPLN. INFO.:				
WO 1998-EP7395	W	19981118		

AB The present invention relates to nucleic acid mols. encoding expression products involved in the Responder function, which contributes to the phenomenon of transmission ratio distortion. The present invention also relates to regulatory regions of the genes corresponding to said nucleic acid mols. The mouse T4-complex, a region of approx. 12 cM genetic distance on the proximal part of chromosome 17, contains several loci acting in concert to produce a phenomenon called transmission ratio distortion, indicating the fact that the so-called 1-haplo type form of this chromosomal region has a selective advantage over the wild type form.

in that it is transmitted to the offspring at non-Mendelian ratios of up to 99%. The cDNA sequences of T66B mols. contain MARRK2 kinase and rsk3 kinase homol. regions. T66Bk-2 cDNA contains only the MARRK2 kinase homol. region, T66k-8 cDNA contains the complete sequence of T66Bk-2 except for a single base deleted resulting in a frameshift. T66k-7 cDNA corresponds to an antisense transcript of a T66Bk family member, and T66k-20 shows strong similarity to the above members of the T66Bk gene family. Addnl. variants of the T66k family are shown from various mouse strains. The Responder function is located in the T66B region, is expressed in testis,

and is expressed during spermiogenesis. Thus, the 1-Responder may act as a component of a signaling cascade involved in sperm motility and/or fertilization of oocytes and relates to methods of influencing transmission ratio. The present invention further relates to recombinant DNA mols. and vectors comprising said nucleic acid mols. and/or regulatory regions as well as to host cells transformed therewith. Addnl. the present invention relates to transgenic animals comprising said nucleic acid mols., recombinant DNA mols. or vectors stably integrated into their genome. The various embodiments of the invention have a significant impact on breeding strategies by allowing for the specific selection of genetic traits and in particular of sex. Further, the present invention finds applications in the development of contraceptives.

L9 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999.166721 CAPLUS
DOCUMENT NUMBER: 130.205932

TITLE: Site-specific recombination in eukaryotes and useful constructs

INVENTOR(S): O'Germain, Stephen; Wahl, Geoffrey
PATENT ASSIGNEE(S): The Salk Institute for Biological Studies, USA
SOURCE: PCT Int. Appl. 54 pp.

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY AOC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9910488	A1	19990304	WO 1998-US17652	19980828
W. AL, AM, AT, AU, AZ, BA, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GR, GU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, CA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9892090	A1	19990316	AU 1998-92090	19980828
PRIORITY APPLN. INFO.:				
US 1997-919501	US	19970828		
WO 1998-US17652	WO	19980828		

AB Site-specific recombinases provide a means of efficiently manipulating chromosomal sequences in mammalian cells in culture. Five lines of transgenic mice contg. a fusion gene encoding the mouse prolinease 1 gene promoter and the Cre recombinase gene, ProCre, showed high levels of Cre-mediated recombination in the germline, but did not show appreciable recombination in other tissues. In other transgenic mice contg. a Cre targeting construct and the ProCre construct, between 80-100% of the progeny inherited the Cre-recombined target. When ES cells from the ProCre line were

transfected with vectors containing a bxp⁺ targeting construct, clones in which the bxp⁺ sites remained functional were readily isolated. These data establish that ProCre nuclear acid constructs will facilitate the production of stable, conditional or tissue-specific mutations in mice as well as the production and analysis of mice with recombinase-conditional lethal alleles.

REFERENCE COUNT: 11

REFERENCE(S): (1) Abdem, M., Molecular and Cellular Biology 1997, V17(2), P857 CAPLUS

(2) Dab, E., Proc Natl Acad Sci USA 1991, V88(23), P10538 CAPLUS

(3) Eysel, Y., Plant Cell 1995, V7, P373 CAPLUS

(4) Oouchi, H., Mol Gen Genet 1995, V247(6), P653 CAPLUS

(6) O'Gorman, S., Proc Natl Acad Sci USA 1997, V94(26), P14602 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V. DUPLICATE 1

ACCESSION NUMBER: 1999251884 EMBASE

TITLE: Efficient liver-specific deletion of a fixed human angiotensinogen transgene by adenoviral delivery of Cre recombinase in vivo.

AUTHOR: Stee D.E.; Davidson R.L.; Haskell R.E.; Davidson B.L.; Sigmund C.D.

CORPORATE SOURCE: C.D. Sigmund, Int. Med./Physiol./Biophysics Dept., 2191

SOURCE: Medical Laboratory, Univ. of Iowa Coll. of Medicine, Iowa City, IA 52242, United States; curt-sigmund@uiowa.edu (21285-21280).

Refs: 40

ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Tissue-specific ablation of gene function is possible in vivo by the Cre-bxp⁺ recombinase system. We generated transgenic mice containing a human angiotensinogen gene flanked by bxp⁺ sites (haGT(bxn)). To examine the physiologic consequences of tissue-specific

bas of angiotensinogen gene function in vivo, we constructed an adenovirus expressing Cre recombinase. Studies were performed in several independent lines of haGT(bxn) mice before and after intravenous administration of AdCre caused a significant decrease in circulating angiotensinogen and markedly blunted the pressor response to administration of purified recombinant human renin. Southern blot analysis of genomic DNA from various organs revealed that the Cre-mediated deletion was liver-specific. Further analysis revealed the absence of full-length human angiotensinogen mRNA and protein in the

liver but not the kidney of AdCre mice, consistent with the liver being the target for adenoviruses administered intravenously. These studies demonstrate that extra-hepatic sources of angiotensinogen do not contribute significantly to the circulating pool of angiotensinogen and provide proof-of-principle that the Cre-bxp⁺ system can be used effectively to examine the contribution of the systemic and renin-angiotensin system to normal and pathological regulation of blood pressure.

L9 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999367362 CAPLUS

DOCUMENT NUMBER: 131:39439

TITLE: Regulation of GATA-4 and AP-1 in transgenic mice overexpressing cardiac calsequestrin

AUTHOR(S): Suzuki, Y. J.; Ikeda, T.; Shi, S. S.; Kikita, K.; Kobayashi, Y. M.; Morad, M.; Jones, L. R.; Blumberg, J. B.

CORPORATE SOURCE: Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA, 02111, USA

SOURCE: Cell Calcium (1999) 25(6), 401-407

CODEN: OECADY; ISSN: 0143-4160

PUBLISHER: Churchill Livingstone

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Transgenic mouse hearts overexpressing the Ca²⁺-binding protein calsequestrin (CSQ) have an accompanying 10-fold increase in the sarcoplasmic reticulum (SR) Ca²⁺-load, however, exhibits slow and small Ca²⁺-induced Ca²⁺-release. Such slow kinetics of Ca²⁺-release may have activated excitation-transcription coupling as CSQ overexpressing hearts have induced levels of NFAT and GATA-4 activities and higher levels of c-fos mRNA and c-fos protein compared to those of non-transgenic littermates. Adaptive responses, however, appear to downregulate transcriptional regulators controlling c-fos gene including serum response factor and Ca²⁺-calmodulin response element-binding protein. CSQ-overexpressing hearts also had decreased levels of c-Jun protein, resulting in downregulated AP-1 activity. The mRNA levels of angiotensin II type 1a receptor which requires AP-1 and GATA-4 for gene transcription was suppressed in CSQ overexpressing hearts. These results demonstrate that CSQ can regulate GATA-4- and AP-1-dependent transcriptional events, indicating the existence of SR-nuclear circuits of signal transduction in adult cardiac muscle.

REFERENCE COUNT: 29

REFERENCE(S): (1) Boelman, M., Cell 1993, V63, P875 CAPLUS

(2) Bradford, M., Anal Biochem 1976, V72, P248 CAPLUS

(3) Dolmetsh, R., Nature 1997, V386, P855 CAPLUS

(4) Friedl, M., Nucleic Acid Res 1981, V9, P6505 CAPLUS

(5) Garner, M., Nucleic Acid Res 1981, V9, P3047 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998287821 CAPLUS

DOCUMENT NUMBER: 129:37165

TITLE: A cyclic AMP response element in the angiotensin-converting enzyme gene and the transcription factor CREM are required for transcription of the mRNA for the testicular isoenzyme

AUTHOR(S): Kessler, Sean P.; Rowe, Theresa M.; Bandy, Julie A.; Erickson, Robert P.; Sen, Ganesh C.

CORPORATE SOURCE: Department Molecular Biology, Lerner Institute, Cleveland Clinic Foundation, Cleveland, OH, 44195 USA

SOURCE: J Biol Chem (1998) 273(16), 9971-9975

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The angiotensin-converting enzyme (ACE) gene produces two species from tissue-specific promoters. The transcription start site of the mRNA for the smaller testicular isoenzyme (ACE^T) is located within an

intron of the larger transcription unit that encodes the pulmonary isoenzyme (ACE^P). The authors have previously demonstrated that a 298-base pair DNA fragment, 5' to the rabbit ACE^T mRNA transcription initiation site, can activate the testicular expression of a transgenic reporter gene. In the current study, using the same transgenic reporter system, the authors identified a putative cAMP response element present within this DNA fragment to be absolutely essential for transcriptional activation. Moreover, the authors observed that ACE^T mRNA was not expressed in the testes of mice homozygous for a null mutation in the transcription factor CREM. However, in the same mice, ACE^P mRNA was abundantly expressed in the lung. Our observations indicate that ACE^T mRNA expression in the testes is regulated by the putative cAMP response element present 5' to the transcription start site and the corresponding transcription factor CREM.

L9 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997499250 CAPLUS

DOCUMENT NUMBER: 127:172237

TITLE: Neuroendocrine cell lines for efficient synthesis and secretion of foreign proteins

INVENTOR(S): Newgard, Christopher B.; Halban, Philippe A.; Normington, Karl D.; Clark, Samuel A.; Thigpen, Anne E.; Quade, Christian; Kruse, Fred; et al.

PATENT ASSIGNMENT(S): Board of Regents, University of Texas System, USA.

SOURCE: Biotechnology, Inc.; Newgard, Christopher B.; Halban, Philippe A.; Normington, Karl D.; Clark, Samuel A.; Thigpen, Anne E.; PCT Int. Appl., 278 pp.

CODEN: PXXDZ

DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 9726334 A1 1997/0724 WO 1997/US760 1997/0117

W. AL, AM, AT, AU, AZ, BA, BG, BR, BY, CA, CH, CN, CU, CZ,

DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC,

LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,

PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ,

VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB,

GR,

IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML,

MR, NE, SN, TD, TG

US 6087129 A 2000/0711 US 1996-569028 1996/0119

CA 2246268 A 1997/0724 CA 1997-224628 1997/0117

AU 9718309 A1 1997/0811 AU 1997-18309 1997/0117

EP 876484 A1 1998/1111 EP 1997-903838 1997/0117

PT, R, AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE, MC,

IE, FI

PRIORITY APPL. INFO.: US 1996-589028 A2 1996/0119

WO 1997/US760 W 1997/0117

AB Methods of constructing neuroendocrine cell lines capable of high-level

expression of a foreign gene and efficient secretion of the gene product are described. Such a cell line has the ability to express a gene that encodes a major cell gene product specific to the cell line. The host cell machinery normally used to produce this polypeptide then becomes

spare prodn. capacity for the synthesis of the foreign gene product. These lines or the gene products have a no. of therapeutic uses, e.g. in treatment of disease, in the development of vaccines. The gene may be expressed from a strong animal or animal virus promoter and preferably is an analog of the major gene inactivated in the development, e.g. a human gene expressed in an insulinome-derived line. This makes use of the

endogenous accessory systems for post-translational modification and secretion of the gene product. Stable expression of the human insulin gene in rat insulinoma cells that have had the endogenous insulin gene insertionally inactivated is demonstrated. These cells also efficiently secrete human insulin and accurately processed the human proinsulin to insulin.

L9 ANSWER 7 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI.

B.V.DUPPLICATE 2

ACCESSION NUMBER: 97368207 EMBASE

DOCUMENT NUMBER: 1997368207

TITLE: Expression of testis angiotensin-converting

enzyme is mediated by a cyclic AMP responsive element.

AUTHOR: Esther C.R. Jr.; Semeniuk D.; Mento E.M.; Zhou Y.;

Overbeek P.A.; Bernstein K.E.

CORPORATE SOURCE: Dr. K.E. Bernstein, WMB, Department of Pathology, Emory

University, Atlanta, GA 30322, United States

SOURCE: Laboratory Investigation, (1997) 77/5 (463-486).

Ref: 33

ISSN: 0023-6837 CODEN: JAINAW

COUNTRY: United States

DOCUMENT TYPE: Journal Article

FILE SEGMENT: 021 Developmental Biology and Teratology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Testis angiotensin-converting enzyme (testis ACE), an ACE isozyme that plays an important role in male fertility, is transcribed from a unique promoter active only in developing spermatids. In vitro analysis suggests the importance of a cyclic AMP response element (CRE)-like region within the testis ACE promoter, and similar DNA motifs are important in the expression of a variety of testis-specific genes. In the present study, we examined the effects of mutations in the CRE-like element on testis ACE promoter activity in vivo using transgenic mice. Disruption of this element reduced reporter gene expression to near background levels. In contrast, conversion of the CRE-like element to a consensus CRE-binding site resulted in high level expression of the reporter gene specifically in the testis. These experiments prove that the CRE-like element is essential for testis ACE promoter activity, although it does not appear to be responsible for its tissue specificity. These data provide insight into how a phenotypically differentiated tissue, ie, male germ cells, regulate tissue-specific gene expression.

L9 ANSWER 8 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI.

B.V.DUPPLICATE 3

ACCESSION NUMBER: 96241517 EMBASE

DOCUMENT NUMBER: 1996241517

TITLE: Species variation in the testicular angiotensin

converting enzyme promoter studied in transgenic mice.

AUTHOR: Erickson R.P.; Kessler S.; Krenning H.; Sen G.C.

CORPORATE SOURCE: Steeb Memorial Children's Res. Ctr., College of Medicine,

University of Arizona, 1501 N. Campbell Avenue, Tucson, AZ

85724, United States

SOURCE: Molecular Reproduction and Development, (1996) 44/3

(324-331)

ISSN: 1040-452X CODEN: MREDEE

COUNTRY: United States

DOCUMENT TYPE: Journal Article

FILE SEGMENT: 021 Developmental Biology and Teratology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB We have studied the control of transcription of the testicular angiotensin converting enzyme (ACE) in normal and transgenic mice. Northern analyses, including a developmental curve and separated germ cells, for ACE1 mRNA suggest predominantly post-meiotic expression. Mice transgenic for a construct containing the proximal 288 bp of the rabbit ACE1 promoter, with chimeric phenol acetyl transferase (CAT) as a reporter, showed correct tissue regulation while a 86 bp fragment of the promoter led to no

expression. Many candidate transacting factor binding elements, previously identified as candidate regulators of transcription driving spermatogenesis, are scattered across this 288 bp in the rabbit (but not the mouse) promoter and may lead to tissue specificity. The recent finding that the proximal 91 bp of the mouse ACE1 promoter leads to tissue specific expression of a reporter gene (Howard et al., 1993) emphasizes the difference between the two species and the importance of a cAMP response element (CRE) within this fragment for tissue specific expression. This CRE is conserved in the rabbit promoters we used.

L9 ANSWER 9 OF 9 EMBASE COPYRIGHT 2001 ELSEVIER SCI.

B.V.DUPPLICATE 4

ACCESSION NUMBER: 93006878 EMBASE

DOCUMENT NUMBER: 1993006878

TITLE: Sperm-specific expression of angiotensin

-converting enzyme (ACE) is mediated by a 91-base-pair promoter containing a CRE-like element.

AUTHOR: Howard T.; Balogh R.; Overbeek P.; Bernstein K.E.

CORPORATE SOURCE: Department of Pathology, Emory University, Atlanta, GA

30322, United States

SOURCE: Molecular and Cellular Biology, (1993) 13/1 (18-27).

ISSN: 0270-7306 CODEN: MCEBUD

COUNTRY: United States

DOCUMENT TYPE: Journal Article

FILE SEGMENT: 022 Human Genetics

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The gene encoding the testis isozyme of angiotensin-converting enzyme (testis ACE) is one example of the many genes expressed uniquely during spermatogenesis. This protein is expressed by developing germ cells

late in their development and results from the activation of a sperm-specific promoter that is located within intron 12 of the gene encoding the somatic isozyme of ACE. In vitro transcription, DNAse footprinting, gel shift assays, and transgenic mouse studies have been used to define the minimal testis ACE promoter and to characterize DNA-protein interactions mediating germ cell-specific expression. These studies show that proper cell- and stage-specific expression of testis ACE requires only a small portion of the immediate upstream sequence extending to -31. A critical motif within this core promoter is a cyclic AMP-responsive element sequence that interacts with a testis-specific transactivating factor. Since this putative cyclic AMP-responsive element has been conserved within the testis ACE promoters of different species and is found at the same site in other genes that are expressed specifically in the testis, it may provide a common mechanism for the recognition of sperm-specific promoters.

=> s thomas k7/au
L10 3992 THOMAS K7/AU

=> d his

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FILE EMBASE, BIOSIS, LIFESCI, MEDLINE, CAPLUS: ENTERED AT
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JUN 2001
L1 0 S CRELOXIP
L2 11929 S ORE
L3 160055 S TRANSGENP
L4 1391 S L2 AND L3
L5 61 S L4 AND (GENE THERAPY)
L6 38 DUP REM L5 (23 DUPLICATES REMOVED)
L7 0 S L4 AND TACE
L8 24 S L4 AND ANGIOTENSIN
L9 9 DUP REM L8 (15 DUPLICATES REMOVED)
L10 3992 S THOMAS K7/AU

=> s il0 and M
L11 1 L10 AND L4

=> d il1 ilb abs

L11 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:12604 CAPLUS
DOCUMENT NUMBER: 134:81749
TITLE: Method for deleting a nucleic acid sequence in a
specified tissue from a DNA introduced into the
organism

INVENTOR(S): Thomas, Kirk R.; Bernstein, Kenneth E.;
Burling, Michaelne; Greer, Joy; Capocchi, Mario
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE
WO 2001000809 A1 20010104 WO 2000-US-17828 20000629
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE,
CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-141267 P 19990630
AB The present invention is directed to a method for deleting DNA
sequences

in a tissue specific manner. In one embodiment, DNA sequences are
specifically deleted in germline tissue. In a second embodiment, DNA
sequences are specifically deleted in desired somatic tissue. The

present invention is further directed to a nucleic acid mol. for use in the
method. More specifically, a nucleic acid mol. is provided by the
present invention which comprises (a) a recombinase site, (b) a tissue-specific
promoter, (c) a recombinase gene, (d) a foreign DNA, and (e) a
recombinase site. The nucleic acid mol. may further comprise a gene which is
desired to be incorporated into and expressed in a transgenic organism.
The method can be used in both plants and animals, and has many
applications as described herein.

REFERENCE COUNT: 1
REFERENCE(S): (1) Kitamoto; Biochemical and Biophysical
Research
Communications 1996, V222(3), P742 CAPLUS

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'AI IS NOT A VALID FIELD CODE
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'AI IS NOT A VALID FIELD CODE
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L12 0 BERNSTEIN K7/AI

=> s bernstein k7/au
L13 695 BERNSTEIN K7/AU
=> s il3 and M
L14 10 L13 AND L4

=> dup rem il4
PROCESSING COMPLETED FOR L14
L15 3 DUP REM L14 (7 DUPLICATES REMOVED)

=> d il5 1-3 ilb abs

L15 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:12604 CAPLUS
DOCUMENT NUMBER: 134:81749
TITLE: Method for deleting a nucleic acid sequence in a
specified tissue from a DNA introduced into the
organism
INVENTOR(S): Thomas, Kirk R.; Bernstein, Kenneth E.;
Burling, Michaelne; Greer, Joy; Capocchi, Mario
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

WO 2001000809 A1 20010104 WO 2000-US-17828 20000629
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,
CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
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HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
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ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE,
CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-141267 P 19990630
AB The present invention is directed to a method for deleting DNA
sequences

in a tissue specific manner. In one embodiment, DNA sequences are
specifically deleted in germline tissue. In a second embodiment, DNA
sequences are specifically deleted in desired somatic tissue. The
present invention is further directed to a nucleic acid mol. for use in the
method. More specifically, a nucleic acid mol. is provided by the
present invention which comprises (a) a recombinase site, (b) a tissue-specific
promoter, (c) a recombinase gene, (d) a foreign DNA, and (e) a
recombinase site. The nucleic acid mol. may further comprise a gene which is
desired to be incorporated into and expressed in a transgenic organism.
The method can be used in both plants and animals, and has many
applications as described herein.

REFERENCE COUNT: 1
REFERENCE(S): (1) Kitamoto; Biochemical and Biophysical
Research
Communications 1996, V222(3), P742 CAPLUS

L15 ANSWER 2 OF 3 EMBASE COPYRIGHT 2001 ELSEVIER SCI.
B.V. DUPLICATE 1
ACCESSION NUMBER: 97368207 EMBASE
DOCUMENT NUMBER: 1997368207
TITLE: Expression of testis angiotensin-converting enzyme is
mediated by a cyclic AMP responsive element.
AUTHOR: Overbeek P.A.; Bernstein K.E.
CORPORATE SOURCE: Dr. K.E. Bernstein, WMB, Department of
Pathology, Emory
University, Atlanta, GA 30322, United States
SOURCE: Laboratory Investigation, (1997) 77(5):463-469.
Refs: 33
ISSN: 0023-6837 CODEN: LAJN4W
COUNTRY: United States
DOCUMENT TYPE: Journal Article
FILE SEGMENT: 021 Developmental Biology and Teratology

LANGUAGE: English
SUMMARY LANGUAGE: English
AB Testis angiotensin-converting enzyme (testis ACE), an ACE isozyme that plays an important role in male fertility, is transcribed from a unique promoter active only in developing spermatids. In vitro analysis suggests the importance of a cyclic AMP response element (CRE)-like region within the testis ACE promoter, and similar DNA motifs are important in the expression of a variety of testis-specific genes. In the present study, we examined the effects of mutations in the CRE-like element on testis ACE promoter activity in vivo using transgenic mice. Disruption of this element reduced reporter gene expression to near background levels. In contrast, conversion of the CRE-like element to a consensus CRE-binding site resulted in high level expression of the reporter gene specifically in the testis. These experiments prove that the CRE-like element is essential for testis ACE promoter activity, although it does not appear to be responsible for its tissue specificity. These data provide insight into how a phenotypically differentiated tissue, ie, male germ cells, regulate tissue-specific gene expression.

L15 ANSWER 3 OF 3 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B/DUPLICATE 2
ACCESSION NUMBER: 93006878 EMBASE
DOCUMENT NUMBER: 1993006878
TITLE: Sperm-specific expression of angiotensin-converting enzyme
(AACE) is mediated by a 91-base-pair promoter containing a CRE-like element.
AUTHOR: Howard T.; Babgh R.; Overbeek P.; Bernstein K.E.
CORPORATE SOURCE: Department of Pathology, Emory University, Atlanta, GA
SOURCE: 30322, United States
Molecular and Cellular Biology (1993) 13(1 (18-27).
ISSN: 0270-7306 CODEN: MCEBD4
COUNTRY: United States
DOCUMENT TYPE: Journal Article
FILE SEGMENT: 022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The gene encoding the testis isozyme of angiotensin-converting enzyme (testis ACE) is one example of the many genes expressed uniquely during spermatogenesis. This protein is expressed by developing germ cells late in their development and results from the activation of a sperm-specific promoter that is located within intron 12 of the gene encoding the somatic isozyme of ACE. In vitro transcription, DNase footprinting, gel shift assays, and transgenic mouse studies have been used to define the minimal testis ACE promoter and to characterize DNA-protein interactions mediating germ cell-specific expression. These studies show that proper cell- and stage-specific expression of testis ACE requires only a small portion of the immediate upstream sequence extending to -

91.
A critical motif within this core promoter is a cyclic AMP-responsive element sequence that interacts with a testis-specific transactivating factor. Since this putative cyclic AMP-responsive element has been conserved within the testis ACE promoters of different species and is found at the same site in other genes that are expressed specifically in the testis, it may provide a common mechanism for the recognition of sperm-specific promoters.

=> s bunling m7au
L16 85 BUNTING M7AU
=> s l16 and l4
L17 11.16 AND L4
=> d l17 tab abs
L17 ANSWER 1 OF 1 CARLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:12604 CARLUS
DOCUMENT NUMBER: 134.81749
TITLE: Method for deleting a nucleic acid sequence in a specified tissue from a DNA introduced into the organism
INVENTOR(S): Thomas, Kirk R.; Bernstein, Kenneth E.; Bunting, Michaeline, Greer, Joy; Capocchi, Mario
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PLYX02
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:
PATENT NO. KIND DATE APPLICATION NO. DATE
WO 2001000809 A1 2001/01/04 WO 2000-US-17828 2000/06/29
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, NI, SN, TD, TG
PRIORITY APPL. INFO.: US 1999-141267 P 1999/06/30
AB The present invention is directed to a method for deleting DNA sequences in a tissue specific manner. In one embodiment, DNA sequences are specifically deleted in germline tissue. In a second embodiment, DNA sequences are specifically deleted in desired somatic tissue. The present invention is further directed to a nucleic acid mol. for use in the

method. More specifically, a nucleic acid mol. is provided by the present invention which comprises (a) a recombinase site, (b) a tissue-specific promoter, (c) a recombinase gene, (d) a foreign DNA, and (e) a recombinase site. The nucleic acid mol. may further comprise a gene which is desired to be incorporated into and expressed in a transgenic organism. The method can be used in both plants and animals, and has many applications as described herein.

REFERENCE COUNT: 1
REFERENCE(S): (1) Kitamoto; Biochemical and Biophysical Research Communications 1996, V222(3), P742 CARLUS
=> s greer j4u
L18 292 GREER J4U
=> s l18 and l4
L19 0.1.18 AND L4
=> s l18 and bxp
L20 0.1.18 AND LOXP
=> s capocchi m7au
L21 449 CAPECCHI M7AU
=> s d1 and l4
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PROCESSING COMPLETED FOR L22
L23 3 DUP REM L22 (4 DUPLICATES REMOVED)
=> d l23 1-3 tab abs
L23 ANSWER 1 OF 3 CARLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:12604 CARLUS
DOCUMENT NUMBER: 134.81749
TITLE: Method for deleting a nucleic acid sequence in a specified tissue from a DNA introduced into the organism
INVENTOR(S): Thomas, Kirk R.; Bernstein, Kenneth E.; Bunting, Michaeline, Greer, Joy; Capocchi, Mario
PATENT ASSIGNEE(S): University of Utah Research Foundation, USA
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PLYX02
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:
PATENT NO. KIND DATE APPLICATION NO. DATE
WO 2001000809 A1 2001/01/04 WO 2000-US-17828 2000/06/29
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, AY, KG, KZ, MD, RU, TJ, TM, RW, GH, GM, KE, LS, MM, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG, PRIORITY APPLN. INFO.: US 1999-141267 P 19990630

AB The present invention is directed to a method for deleting DNA sequences in a tissue specific manner. In one embodiment, DNA sequences are specifically deleted in germline tissue. In a second embodiment, DNA sequences are specifically deleted in desired somatic tissue. The present invention is further directed to a nucleic acid mol. for use in the method. More specifically, a nucleic acid mol. is provided by the present invention which comprises (a) a recombinase site, (b) a tissue-specific promoter, (c) a recombinase gene, (d) a foreign DNA, and (e) a recombinase site. The nucleic acid mol. may further comprise a gene which is to be incorporated into and expressed in a transgenic organism. The method can be used in both plants and animals, and has many applications as described herein.

REFERENCE COUNT: 1

REFERENCE(S): (1) Kilmico, Biochemical and Biophysical Research Communications 1996, V22(3), P742 CAPLUS

L23 ANSWER 2 OF 3 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V. DUPLICATE 1

ACCESSION NUMBER: 2000433813 EMBASE

TITLE: Illegitimate Cre-dependent chromosome rearrangements in transgenic mouse spermatids.

AUTHOR: Schmidt E.E.; Taylor D.S.; Prigge J.R.; Barnett S.; Capocchi M.R.

CORPORATE SOURCE: M.R. Capocchi, Howard Hughes Medical Institute, University of Utah, 15 North 2030 East, Salt Lake City, UT 84112-5331, United States, marco.capocchi@genetics.utah.edu

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (5 Dec 2000) 97(25) (13702-13707), Reiss, 45

ISSN: 0027-8424 CODEN: PNASAS6

COUNTRY: United States

DOCUMENT TYPE: Journal Article

FILE SEGMENT: 029 Critical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The bacteriophage P1 Cre/loxP system has become a powerful tool for in vivo manipulation of the genomes of transgenic mice. Although in vitro studies have shown that Cre can catalyze recombination between cryptic 'pseudo-xP' sites in mammalian

genomes, to date there have been no reports of loxP-site infidelity in transgenic animals. We produced lines of transgenic mice that use the mouse Protamine 1 (Prm1) gene promoter to express Cre recombinase in postmeiotic spermatids. All male founders and all Cre-bearing male descendants of female founders were sterile; females were unaffected. Sperm counts, sperm motility, and sperm morphology were normal, as was the mating behavior of the transgenic males and the production of two-cell embryos after mating. Mice that expressed similar levels of a derivative transgene that carries an inactive Cre exhibited normal male fertility. Analyses of embryos from matings between sterile Cre-expressing males and wild-type females indicated that Cre-catalyzed chromosome rearrangements in the spermatids that had to abortive pregnancies with 100% penetrance. Similar Cre-mediated, but loxP-independent, genomic alterations may also occur in somatic tissues that express Cre, but, because of the greater difficulty of assessing deleterious effects of somatic mutations, these may go undetected. This study indicates that, following the use of the Cre/loxP site-specific recombination systems in vivo, it is prudent to eliminate or inactivate the Cre recombinase gene as rapidly as possible.

L23 ANSWER 3 OF 3 MEDLINE

ACCESSION NUMBER: 2000129922 MEDLINE

DOCUMENT NUMBER: 20729922 PubMed ID: 10662638

TITLE: Normal limb development in conditional mutants of Fgf4.

AUTHOR: Moon A.M.; Boulter A.M.; Capocchi M.R.

CORPORATE SOURCE: Howard Hughes Medical Institute, Department of Human Genetics, University of Utah School of Medicine, Salt Lake City, UT 84112, USA.

SOURCE: DEVELOPMENT, (2000 Mar) 127 (5) 989-96. Journal code: ECV, 8701744, ISSN: 0950-1991.

PUB. COUNTRY: ENGLAND, United Kingdom

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200004

ENTRY DATE: Entered STN: 20000413

Last Updated on STN: 20000413

Entered MEDLINE: 20000403

AB Fibroblast growth factors (FGFs) mediate multiple developmental signals in vertebrates. Several of these factors are expressed in limb bud structures that direct patterning of the limb. FGF4 is produced in the apical ectodermal ridge (AER) where it is hypothesized to provide mitogenic and morphogenic signals to the underlying mesenchyme that regulate normal limb development. Mutation of this gene in the germline of mice results in early embryonic lethality, preventing subsequent evaluation of Fgf4 function in the AER. A conditional mutant of Fgf4, based on site-specific Cre/loxP-mediated excision of the gene, allowed us to bypass embryonic lethality and directly test the role of FGF4 during limb development in living murine embryos. This conditional mutation was designed so that concomitant with inactivation of the Fgf4 gene by

excision of all Fgf4-coding sequences, a reporter gene was activated in Fgf4-expressing cells, allowing assessment of the site-specific recombination reaction. Although a large body of evidence led us to predict that deletion of Fgf4 gene function in the AER of developing mice would result in abnormal limb outgrowth and patterning, we found that Fgf4 conditional mutants had normal limbs. Furthermore, expression patterns of Shh, Bmp2, Fgf8 and Fgf10 were normal in the limb buds of the conditional mutants. These findings indicate that the previously proposed FGF4-feedback loop is not essential for coordination of murine limb outgrowth and patterning. We suggest that some of the roles currently attributed to FGF4 during early vertebrate limb development may be performed by other AER factors in vivo.

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FILE EMBASE, BIOSIS, LIFESCI, MEDLINE, CAPLUS ENTERED AT 09:18:45 ON 08 JUN 2001

L1 0 S CRELOXP

L2 11929 S CRE

L3 16055 S TRANSGEN

L4 1391 S L2 AND L3

L5 61 S L4 AND (GENE THERAPY)

L6 38 DUP REM L5 (23 DUPLICATES REMOVED)

L7 0 S L4 AND TACE

L8 24 S L4 AND ANGIOGENIN

L9 9 DUP REM L8 (15 DUPLICATES REMOVED)

L10 3992 S THOMAS K7AU

L11 1 S L10 AND L4

L12 0 S BERNSTEIN K7AI

L13 695 S BERNSTEIN K7AU

L14 10 S L13 AND L4

L15 3 DUP REM L14 (7 DUPLICATES REMOVED)

L16 85 S BUNTING M7AU

L17 1 S L16 AND L4

L18 292 S GREER JAU

L19 0 S L18 AND L4

L20 0 S L18 AND LOXP

L21 449 S CAPECCHI M7AU

L22 7 S L21 AND L4

L23 3 DUP REM L22 (4 DUPLICATES REMOVED)

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COST IN U.S. DOLLARS	ENTRY	SINCE FILE SESSION	TOTAL
FULL ESTIMATED COST		127.42	127.57

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) SINCE FILE
TOTAL

CA SUBSCRIBER PRICE	ENTRY	SESSION
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